American Heart Journal

An international publication for the study of the circulation

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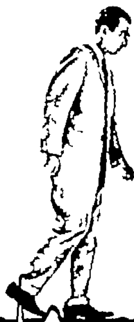
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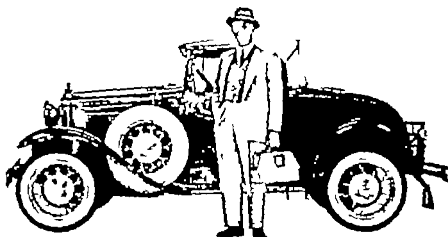
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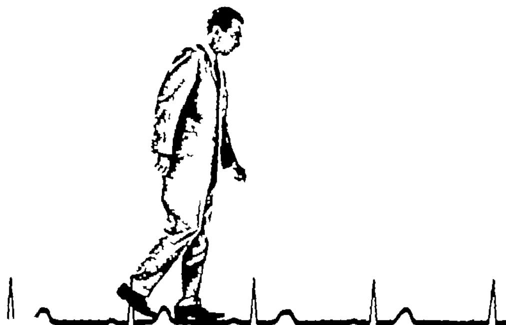
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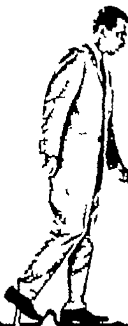
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American Heart Journal

July 1965 Volume 70 Number 1

Editorial

The use of potassium in the treatment of heart disease

*Ernest W. Reynolds, Jr., M.D.**
Ann Arbor, Mich.

Potassium salts are currently used for the treatment of digitalis intoxication, and in heart failure especially where hypokalemia has occurred after the aggressive use of diuretics. They are also used prophylactically to prevent losses of potassium during the long term administration of thiazide diuretics. A few patients with myocardial infarction and coronary artery disease have received potassium along with glucose and insulin. In order to help find the proper place for potassium in the treatment of heart disease, I have undertaken to review what is known in this field in the hope that this might suggest where future research would be rewarding and possibly to forestall unwarranted enthusiasm for any general application of potassium therapy.

Abnormal distribution of potassium in heart disease. Over the past three decades evidence has accumulated showing that cardiac and skeletal muscle of patients dying of congestive failure is abnormally poor in potassium, phosphorous, and magnesium, and that sodium tends to be increased.[1-3] Calhoun and associates[4] further noted that potassium deficiency could be present in one ventricle but not in the other. When myocardial insufficiency resulted in pulmonary congestion, the potassium content of the left ventricle was diminished, and when myocardial insufficiency resulted in hepatic congestion and systemic edema, the potassium content of the right ventricle was decreased. They attributed the loss of potassium to overwork of the involved ventricle, noting that overworked skeletal muscle becomes deficient in potassium. Factors which would contribute to the diffusion of potassium from heart muscle in these circumstances are the associated lack of oxygen and the increased concentration of hydrogen ion.

Brown, Tanner, and Hecht[5] have observed that patients with heart disease have a delayed excretion and a positive balance of orally administered potassium. They thought that potassium should be used with care in patients with heart disease, since these patients do not excrete potassium as rapidly as do normal patients.

Digitalis and loss of potassium. Calhoun and Harrison[6] were first to recognize that

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toxic doses of digitalis lowered the potassium content of ventricular muscle. This fact has now been confirmed by many investigators. Until recently, there was controversy whether therapeutic doses of digitalis caused an ingress of potassium into the heart or egress of it from the heart. Most investigators now concede that therapeutic doses of digitalis produce a small net gain in potassium by cardiac muscle, and that large and toxic doses produce a larger net loss.[9, 8] The amount of potassium lost from cardiac muscle increases with the dose of digitalis glycoside, and Conn[16] has suggested that one action of digitalis is inhibition of an influx mechanism of potassium. It has also been observed that the loss of potassium which occurs after the administration of large or toxic doses of digitalis could be inhibited by the administration of excess potassium.[12]

These ideas have important therapeutic implications. It is obviously desirable to reverse by the administration of potassium the losses of cardiac potassium produced by toxic doses of digitalis. However, the hazard of producing potassium intoxication in this circumstance may be great, since less of the circulating potassium is free to enter the cellular compartment. For instance, Fisch and associates[19] have shown in experimental animals that the tolerance for intravenously administered potassium is related to the quantity of digitoxin administered prior to the injection of potassium. When potassium was administered to animals which had received an intoxicating dose of digitoxin, relatively small amounts of potassium caused a rapid rise in the plasma level of such a magnitude as to result in early cardiac standstill, whereas animals receiving only therapeutic amounts of digitoxin tolerated higher doses of potassium with resultant lower levels of plasma potassium and fewer side effect. These data confirm the concept that large doses of digitalis block the entry of potassium into cells, but also make it evident that the threat to the organism is elevation of the level of extracellular potassium and not the total dose of potassium administered. The data also make clear the potential danger of administering potassium to fully digitalized patients with normal serum potassium, for in this instance the serum potassium may rise to high levels, producing potassium intoxication.

Potassium therapy in digitalis intoxication. Interest in the prevention and treatment of digitalis intoxication was awakened with the report by Lown and associates[21] that the amount of digitalis required to produce digitalis intoxication was related to the level of serum potassium. It was found that smaller doses of digitalis were required to produce intoxication when the serum potassium was low, and high levels of serum potassium had a protective effect in this regard. Prior studies by Loewi[22] in 1918, and Sampson and associates[23] in 1943, had reported that potassium was antagonistic to the toxic effects of digitalis, and that potassium was useful in the treatment of digitalis intoxication in man. Enselberg[7] had observed that increased A-V block was a side effect of such potassium therapy. It soon became evident from other studies that potassium was not a specific antagonist of digitalis. For instance, it was found that potassium would abolish ectopic beats equally well in patients who were receiving digitalis and in those who were not.[23, 24] It was also observed that, when A-V block was produced as the result of digitalis intoxication, administration of potassium did not release the block, but rather potentiated it.[17, 18] It was argued that potassium antagonism of digitalis was based on the rather nonspecific depressing effect of potassium on ectopic rhythm. The conclusion to be reached from these studies is that the ability of potassium to suppress abnormal ectopic rhythm is nonspecific but transiently effective whether or not such abnormal rhythm is the result of digitalis intoxication. Potassium therapy is most useful when digitalis intoxication is the result of potassium depletion, for in this instance the therapeutic margin of safety of digitalis is raised by returning the serum potassium to normal. Caution is advised in the use of potassium therapy when A-V block is a manifestation of digitalis intoxication, since under these circumstances digitalis and potassium are synergistic.

Prophylactic use of potassium with thiazide diuretics. The aggressive use of diuretic agents, such as the thiazide and mercurial

types, initially increases the urinary excretion of potassium as well as sodium and may cause hypokalemia in some patients Weller[21] has presented the argument that the renal tubules of most patients and experimental animals have the ability to counteract the loss of potassium which occurs in the initial phase of thiazide administration and can correct any resulting negative balance of potassium in spite of the continued daily use of these drugs. Prolonged thiazide treatment may result in hypokalemia without significant depletion of the cellular stores of potassium

No evidence is available that potassium therapy is beneficial in heart failure unless there is potassium depletion. As has been pointed out, a shift of potassium from the intracellular to the extracellular compartment in heart failure is caused by the use of large doses of digitalis, and possibly is an early effect of thiazide or other diuretic therapy The data to date do not suggest that this shift is either beneficial or detrimental unless it reaches extreme proportions, in which case it may lead to digitalis intoxication It is common knowledge that when severe potassium depletion occurs after excessive diuresis, supplemental potassium is beneficial Cort and Mathews[22] observed improvement in heart failure when a severe depletion of potassium was corrected. In this circumstance the finding of a low serum potassium a reflection of the level of extracellular potassium is the best guide of the need for supplemental potassium When the need for supplemental potassium arises as indicated by an excessive diuresis, by low serum potassium or by the electrocardiographic changes of hypokalemia, the dose of potassium chloride required will generally be higher (such as 5 to 10 Gm orally in divided doses) than the supplemental and routine dose now commonly prescribed (0.5 to 1 Gm. three times a day) A normal diet generally contains 0 8 to 1.5 Gm of potassium per 1 000[23] calories and is the logical source of supply of potassium at other times.

Potassium toxicity The toxic effects of potassium are related to the concentration of potassium at the site of action as well as to conditions such as oxygen deficit increased concentration of hydrogen ion and decreased concentration of sodium which may alter the normal potassium equilibrium across cell membranes. When potassium is administered the rate of administration becomes important, since this will reflect the peak concentration at the site of action A slow intravenous infusion of potassium in experimental animals induces widespread block in all parts of the heart associated with a reduction in pacemaker automaticity until death occurs by cardiac arrest.[24] Rapid infusions are attended by increased automaticity throughout the heart leading to ventricular premature beats and ventricular fibrillation [25] Wiggers[16] has demonstrated that ventricular fibrillation of the dog's heart can be promptly stopped by large doses of potassium. This paradoxical effect of the infusion of potassium may be explained if it is assumed that the raising of the concentration of potassium to a moderately high level produces a condition of localized block throughout the heart which is favorable for the production of ventricular fibrillation. If the infusion has been rapid enough so that pacemaker automaticity is temporarily enhanced at the same time that local blocks are produced then ventricular fibrillation may be precipitated by a single ventricular beat as suggested by Nahum and Hoff [26] If on the other hand the infusion is slow the phase of increased automaticity is bypassed and only depressed cardiac conduction and decreased pacemaker automaticity are encountered The terminal event in this case is cardiac standstill Still larger doses may slow conduction sufficiently to arrest all cardiac activity whether or not ventricular fibrillation is present. The end result here is profound cardiac depression

Several reports of toxic effect in patients receiving potassium salts for digitalis intoxication are of interest in that they point out the dangers of treating digitalis intoxication with potassium when A V block is one of the chief manifestations and they also point out the fact that the oral use of potassium can be just as hazardous as the intravenous administration According to two reports, potassium was used to treat digitalis intoxication manifest by complete heart block. In both instances cardiac arrest resulted leading to

in one instance and resuscitation with molar sodium lactate in the other.[17] Lown[11] has commented on the dangers of treating digitalis intoxication in patients with heart failure since hyperkalemia may result. He reports on one such patient who received 5 Gm. of potassium chloride daily and who developed atrial standstill and intraventricular block with tall T waves. Saline infusions were effective in reversing this only while the infusion was running. The patient developed pulmonary edema and died with cardiac standstill. Fisch[3] reports one case of transient cardiac arrest after the use of potassium for the treatment of paroxysmal atrial tachycardia with block caused by digitalis. Fisch has also reported that the administration of potassium to a fully digitalized patient with atrial fibrillation led to complete heart block. There have also been reports of serious shocklike symptoms after the oral administration of potassium salts to patients with kidney disease and in patients receiving only 5 Gm. of potassium acetate orally who had no evidence of nitrogen retention.[23]

Conclusions

It is apparent from the toxicity studies available that there is a high risk involved in potassium therapy in patients with renal disease, in patients with heart failure and digitalis intoxication when the serum potassium is normal, and in patients with high-grade A-V block.

There is little evidence to suggest that potassium antagonizes any feature of digitalis intoxication other than digitalis-induced arrhythmias. Potassium therapy is of value in the disturbances in cardiac rhythm due to digitalis intoxication in cases in which A-V block is not the chief manifestation, and in certain disturbances in rhythm which are refractory to quinidine but which are not due to digitalis. Specifically, potassium is useful in the treatment of ventricular premature beats and ventricular tachycardia, but should be withheld in cases of atrial fibrillation with high-grade A-V block and a regular ventricular rhythm. Its use in atrial tachycardia with block has proved to be of value but carries additional risks because of the presence of block. It is contraindicated in the treatment of complete heart block caused by digitalis.

The use of potassium in small daily supplementary doses to prevent the depletion of potassium in patients receiving digitalis and thiazides is unsound in most instances, and the routine use of potassium in this situation should be discontinued. Supplementary potassium may be helpful in the initial phase of diuresis in congestive heart failure and when the serum potassium is lower than normal. There should be no hesitancy about replacing potassium when there is hypokalemia, since most of the severe toxic effects associated with potassium therapy have occurred when it was used in the presence of a normal serum potassium.

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Clinical communications

Mitral atresia

A study of 32 cases

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Atresia of the mitral valve rarely is an isolated cardiac anomaly, and frequently is associated with complex cardiac malformations.[1] Clinically, its presence is usually unsuspected, and in most instances atresia of the mitral valve is discovered only at necropsy. We have reviewed the specimens and clinical data in 32 necropsied cases of mitral atresia from the Cardiovascular Registry of The Charles T. Miller Hospital and University of Minnesota. The 32 cases fell into two groups, based on the clinical and pathologic findings. In the first group were those cases of mitral atresia associated with hypoplasia of the left-sided cardiac structures. A short period of survival characterized the patients in this group. In the other group, in all except one case, mitral atresia, as has been noted by Edwards and Fontana,[2] coexisted with transposition of the great vessels and common ventricle.

It is the purpose of this communication to present the essential anatomic findings in each group. Also, from the available clinical material, an analysis is made of those features which may lead to the clinical diagnosis of mitral atresia and of associated malformations.

Pathologic anatomy and comment

Anatomically, in both groups certain features are shared. The mitral atresia is usually represented by a blind dimple in the floor of the left atrium (Fig. 1,*a* and *b*) and usually no mitral valvular tissue is grossly recognizable (Fig. 1,*c*). Some type of interatrial communication is usual. Commonly, the interatrial communication is created by herniation and prolapse of the normal valve of the foramen ovale into the right atrial cavity, as described by Dolgopol[3] and others[4-6] (Figs. 1,*c* and 2,*b*). Another form of interatrial communication encountered is a true atrial septal defect at the fossa ovalis, resulting from a con-

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Fig 1 a, Opened left atrium (L.A.) and transversely cut blind, minute left ventricle (L.V.) containing blood clot in case of coexistent mitral and aortic atresia (Group I Type A). D "Dimple" at the expected location of mitral valve (mitral atresia). A.A Left atrial appendage. P V Pulmonary vein. V F.O Valve of the foramen ovale. b Opened left atrium (L A) in case of coexistent mitral and aortic atresia (Group I Type A). A.S.D Atrial septal defect at the fossa ovalis. D Dimple at the expected location of mitral valve (mitral atresia). P V : Ostia of pulmonary veins. A.A Left atrial appendage. c, Opened left atrium (L.A) in case of mitral atresia with patent but hypoplastic aortic valve (Group I Type B). The probe is in the interatrial communication created by herniation and prolapse of the valve of the foramen ovale (V F.O) into the right atrial cavity P V Pulmonary vein. A.A Left atrial appendage. Mit. Atr Mitral atresia at the expected location of mitral valve without dimple

genitally short or multifenestrated valve of the foramen ovale (Figs. 1,b and 2,a) Rarely a common atrium is present. Another phenomenon, but uncommon is that the foramen ovale is prematurely closed In all cases, the left atrial chamber is generally small, with a thickened endocardium (Fig 1) whereas the right atrium is enlarged. The tricuspid orifice, although wide, is normally formed

The major pathologic differences among hearts with mitral atresia are based upon the presence or absence of (1) hypoplasia of the left-sided cardiac atri)



Fig. 2. Diagrammatic portrayal of the interatrial communication in mitral atresia. a, True atrial septal defect at the fossa ovalis. b, Interatrial communication created by herniation and prolapse of the valve of the foramen ovale into the right atrial cavity (R.A.). S.V.C. and I.V.C., Superior and inferior venae cavae, respectively. L.A., Left atrium.

tricular septal defect, and (3) transposition of the great vessels. Taking into account these differences, a classification is offered (Table I).

Group I. Great vessels normally interrelated and hypoplasia of left-sided cardiac structures. This group contained 24 of the 3? cases of this study. It is subdivided into Types A and B on the basis of the nature of the aortic valve. In Type A (14 cases) the aortic valve was atretic. The left ventricle was a tiny blind cavity. The ventricular septum was intact in 13 cases, and a ventricular septal defect was present in the fourteenth case. In Type B (10 cases) the aortic valve was patent but hypoplastic, and the left ventricle was small but not so hypoplastic as that in Type A. In all specimens of Group I in which the ductus arteriosus was available for exami-

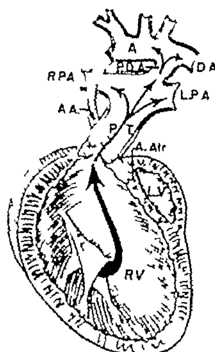


Fig. 3. Diagrammatic portrayal of the arterial circulation in persistent mitral and aortic atresia without ventricular septal defect (Group I, Type A1). The blood in the right atrium is delivered into the right ventricle (R.V.), then is propelled into the enlarged pulmonary trunk (P.T.) and then in turn into the left (L.P.A.) and right (R.P.A.) pulmonary branches and the patent ductus arteriosus (P.D.A.). From the latter vessel blood reaches the descending aorta (D.A.) and flows in the usual manner, whereas in the aortic arch (A) and ascending aorta (A.A.) the blood flows in a retrograde direction. The left ventricle (L.V.) is a minute blind chamber excluded from the circulation. The aortic valve is atretic (A. Atr.). The coronary arteries are supplied by the ascending aorta.

Table I. Classification of mitral atresia

Group I	Great vessels normally interrelated and hypoplasia of the left-sided cardiac structures
Type A	Aortic valvular atresia with markedly hypoplastic left ventricle
	1. With intact ventricular septum
	2. With ventricular septal defect
Type B	Aortic valvular and left ventricular hypoplasia
	1. With intact ventricular septum
	2. With ventricular septal defect
Group II	Great vessels transposed
Type A	Common ventricle
	1. With inverted infundibulum
	2. With noninverted infundibulum
Type B	Two ventricles present

nation it was found to be patent. In both types there was a relatively frequent occurrence of aortic coarctation and anomalies of the pulmonary veins. Atresia of the ostium of the coronary sinus, or persistent left superior vena cava, also occurred frequently.

TYPE A AORTIC VALVULAR ATRESIA WITH MARKEDLY HYPOPLASTIC LEFT VENTRICLE (See Figs. 3 and 4,*a*) In the presence of coexistent mitral and aortic valvular atresia the left ventricle is a minute isolated "blind" chamber and lies hidden near the posterosuperior portion of the left

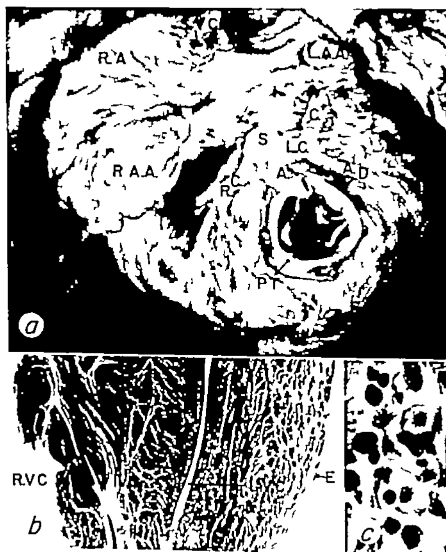


Fig. 4 a, Great vessels viewed from above in coexistent mitral and aortic atresia (Group I Type A1). Note difference between enlarged pulmonary trunk (*P.T.*) and hypoplastic ascending aorta (*A.*), as well as between large right atrial appendage (*R.A.A.*) and small left atrial appendage (*L.A.A.*). Right (*R.C.*) and left (*L.C.*) coronary arteries, the latter with its anterior descending (*A.D.*) and circumflex (*C.*) branches. Coronary arteries arise above the blind aortic sac (*S.*). *R.A.*, Enlarged right atrium. *S.V.C.*, Superior vena ca... *b*, Photomicrograph of minute blind left ventricle in coexistent mitral and aortic atresia (Group I Type A1). *E.*, Epicardium of the free wall of the left ventricle. *L.V.C.*, Slit-like left ventricular cavity. *V.S.*, Ventricular septum. *R.V.C.*, Right ventricular cavity. Elastic tissue stain. ×23. *c*, Photomicrograph of the inflammatory focus in the blind root of the aorta in coexistent mitral and aortic atresia. Hematoxylin-eosin stain. ×600

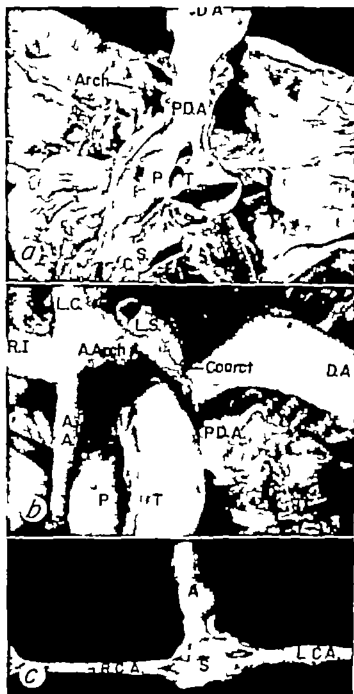


Fig. 5. *a*, Coexistent mitral and aortic atresia (Group I, Type A1). Hypertrophied right ventricle with its characteristic landmark, the crista supraventricularis (*C.S.*). The enlarged pulmonary trunk (*P.T.*) is in continuity with the patent ductus arteriosus (*P.D.A.*), of which the internal surface is grossly corrugated, and descending aorta (*D.A.*). The aortic arch is hypoplastic. *b*, Great vessels in coexistent mitral and aortic valvular atresia (Group I, Type A1). The enlarged pulmonary trunk (*P.T.*) is in continuity with patent ductus arteriosus (*P.D.A.*) and descending aorta (*D.A.*). The ascending aorta (*A.A.*) is extremely hypoplastic. The normal aortic arch (*A.Arch*) gives rise normally to the innominate (*R.I.*), left common carotid (*L.C.*), and left subclavian (*L.S.*) arteries. Coarctation of the aorta (*Coarct.*) is present distal to the left subclavian artery and opposite the patent ductus arteriosus. *c*, Hypoplastic ascending aorta (*A*) with its blind sac (*S*) and right (*R.C.A.*) and left (*L.C.A.*) coronary arteries in coexistent mitral and aortic atresia (Group I, Type A1).

cardiac border as noted by Trillat and Revol[7] in 1935. It was identified by incision of the myocardium immediately to the left of the anterior descending coronary artery and below the left atrial dimple (Fig. 1,*a*). Similar to the case reported by Lev[4] and Noonan and Nadas,[8] the endocardium of the left ventricle was normal in 9 cases (Fig. 4,*b*) and slightly thickened in others. The minute left ventricle contained a blood clot in 4 instances in concert with the findings of Newerla[10] and Lumb and Dawkins.[11] This was explained by the histologic finding of persistent myocardial sinusoids communicating with the left ventricular cavity. As reported by others,[11,12] the ventricular septum was often intact. In 13 cases there was no ventricular septal defect. In 4 of the 14 cases histologic investigation showed some remnants of inflammatory process in the myocardium (Fig. 4,*c*). The right ventricle was large, thick walled, and occupied almost the whole of the ventricular mass (Fig. 5,*a*). The pulmonary trunk was enlarged and in continuity with the patent ductus arteriosus and descending aorta (Figs. 4,*a* and 5,*a* and *b*). The ascending aorta was extremely hypoplastic (4,*a* and 5,*b* and *c*). The coronary arteries arose distal to the atretic aortic valve (Figs. 4,*a* and 5,*c*). A detailed discussion of the pathologic anatomy of these 14 cases is the basis of a separate report.[13]

TYPE B. AORTIC VALVULAR AND LEFT VENTRICULAR HYPOPLASIA. Ten of the 24 cases of mitral atresia in Group I showed patency but hypoplasia of the aortic valve and the left ventricle although

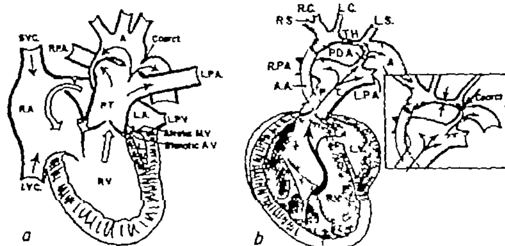


Fig. 6. *a*, Diagrammatic portrayal of circulation in mitral atresia with hypoplastic stenotic aortic valve and with intact ventricular septum (Group I, Type B1). Blood from superior (*S.V.C.*) and inferior (*I.V.C.*) venae cavae is delivered into the enlarged right atrium (*R.A.*). Blood from the small left atrium (*L.A.*) is also delivered into the right atrium, in this situation, through an interatrial communication created by herniation and prolapse of the valve of the foramen ovale into the right atrial cavity. Mixed blood from the right atrium is delivered to the enlarged and hypertrophied right ventricle (*R.V.*) and enlarged pulmonary trunk (*P.T.*) for its left (*L.P.A.*) and right (*R.P.A.*) branches and patent ductus arteriosus. From the latter vessel, blood reaches the descending aorta in a normal manner and the aortic arch (*A.*), ascending aorta, and coronary arteries in a retrograde manner. The left ventricle (*L.V.*) is excluded from circulation since the mitral valve (*M.V.*) is atretic and the aortic valve (*A.V.*), although patent, is competent, thus preventing the blood reaching the left ventricular cavity from the ascending aorta. *L.P.V.*, Left pulmonary vein. *Coarct.*, Coarctation of the aorta opposite the patent ductus arteriosus represents an associated malformation. *b*, Diagrammatic portrayal of central circulation in mitral atresia coexistent with hypoplastic but patent aortic valve and ventricular septal defect (Group I, Type B2). Blood from enlarged and hypertrophied right ventricle (*R.V.*) is delivered (1) to the enlarged pulmonary trunk (*P.T.*) for its right (*R.P.A.*) and left (*L.P.A.*) branches, patent ductus arteriosus (*P.D.A.*) and descending aorta (*A.*) and (2) to the small left ventricle (*L.V.*) through the ventricular septal defect for distrib[ution to] the hypoplastic ascending aorta (*A.A.*). *R.S.* and *L.S.*, Right and left subclavian arteries. *R.C.* and [*L.C.*], Right and left common carotid arteries. Tubular hypoplasia of the aortic arch (*T.H.*) or coarctation [of the aorta] are commonly associated anomalies.

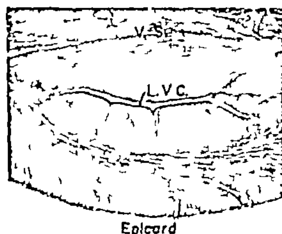
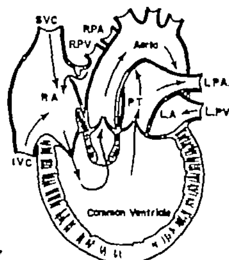


Fig. 7. Photomicrograph of the minute left ventricle in mitral atresia with hypoplastic but competent aortic valve and intact ventricular septum (Group I, Type B). *Epicard*, Epicardium of the free wall of the left ventricle. *L.V.C.*, Minute left ventricular cavity. *V.S.*, Ventricular septum.

hypoplastic was larger than in Type A. In ? cases the aortic valve was of the congenitally bicuspid type. The ascending aorta (except in the one case with intact ventricular septum) was not hypoplastic but the aortic arch usually showed coarctation or tubular hypoplasia. Premature closure of the foramen ovale had occurred *in 4 of these 10 cases. In the presence of an* atretic mitral valve and patent but hypoplastic aortic valve the size of the left ventricle depended upon the presence or absence of a ventricular septal defect (Fig. 6,*a* and *b*). When such a defect was present, as in 9 of these 10 cases, the left ventricle participated in systemic circulation, as noted by Edwards and Rogers[4] and by DuShane.[14] Blood from the right ventricle enters the left ventricle through the ventricular septal defect and from that chamber in turn enters the aorta (Fig. 6,*b*).

In the one case of this type in which the ventricular septum was intact the ascending aorta and coronary arteries, as in Type A, received blood in a retrograde manner ultimately from the patent ductus arteriosus. Similar observations were made by Moore and Menne in 1921. Because of the competent aortic valve the left ventricle still remained excluded from the circulation (Figs. 6,*a* and 7).



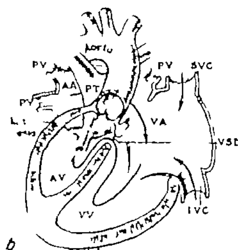


Fig. 8. *a*, Diagrammatic portrayal of the circulation in mitral atresia with transposed great vessels and common ventricle (Group II, Type A). The blood entering into the left atrium (*L.A.*) from the left (*L.P.V.*) and right (*R.P.V.*) pulmonary veins escapes into the right atrium (*R.A.*) through the interatrial communication and is mixed with blood from the superior (*S.V.C.*) and inferior (*I.V.C.*) venae cavae. Blood from the right atrium is delivered to the common ventricle and then propelled to the aorta and pulmonary trunk (*P.T.*) for its right (*R.P.A.*) and left (*L.P.A.*) branches. *b*, Diagrammatic portrayal of the circulation in mitral atresia with transposed great vessels and two ventricles present (Group II, Type B) in a case of situs inversus. Blood from the pulmonary veins (*P.V.*) and superior (*S.V.C.*) and inferior (*I.V.C.*) venae cavae enters the arterial (*A.A.*) and venous (*V.A.*) portions of the common atrium respectively. All blood is then delivered to the venous ventricle (*V.V.*) and further through the ventricular septal defect (*V.S.D.*) to the arterial ventricle (*A.V.*). Both aorta and pulmonary trunk (*P.T.*) arise from the arterial ventricle.

Group II Great vessels transposed Among the 37 cases of mitral atresia, 8 were characterized by the presence of some form of transposition of the great vessels. This group is subdivided into two types according to the anatomic state of the ventricular septum. Thus, in Type A (7 cases) transposed great vessels coexisted with a common ventricle (Fig 8,*a*) whereas in the one case representing Type B two ventricles were present, as was a ventricular septal defect (Fig 8,*b*)

By Keith's[17] definition, a common ventricle exists when both atria communicate with a single ventricular chamber either through two independent valves or through a common atrioventricular canal. Our cases however were similar to those reported by Turner Dudrus,[1] and Walls,[29] in that the mitral valve was atretic, whereas the tricuspid valve alone communicated with the common ventricular chamber In each of the 7 cases of Type A, the aorta arose anterior to the pulmonary trunk from a rudimentary outlet (infundibulum) chamber located at the anterior and basal portion of the common ventricle as noted by Brock.[31]

In Type A, a further subdivision was possible on the basis of inversion or noninversion of the infundibular chamber In the 2 instances in which the infundibular chamber was located at the right, anterior and basal portion of the common ventricle, it was designated to be in a noninverted position as described by Elliott and associates.[32] In these cases, the long axis of the infundibular chamber was directed upward and leftward to the origin of the aorta. In the remainder (5 cases) in which the infundibular chamber was located at the left anterior and basal portion of the common ventricle, it was considered to be in an "inverted" position.[32] In this subgroup the long axis of the inverted infundibular chamber was directed upward and rightward to the origin of the aorta. The inverted type may therefore be considered to be a mirror image of the noninverted type

From the external aspect of the heart, therefore in those cases with a noninverted infundibulum the origin of the great arteries resembled that in complete transposition of the great vessels. In those cases with an inverted infundibulum the origin of the great arteries resembled that in corrected transposition of the great vessels.

TYPE A COMMON VENTRICLE. Among the 7 cases of this type the infundibular chamber was inverted in 5 and noninverted in 2 In 6 of these 7 cases there was obstruction to pulmonary outflow This was represented by pulmonary valvular atresia in 3 by coexistent pulmonary and subpulmonary stenosis in 1 and by subpulmonary stenosis in 2. In the 2 cases with noninverted infundibulum the pulmonary valve was atretic in one, and congenitally bicuspid in the other The pulmonary venous terminations in each case of Type A were normal In each of 5 of the 7 cases a persistent left superior vena cava was present and in 2 of these the right atrial ostium of the coronary sinus was atretic.

TYPE B TWO VENTRICLES PRESENT The single case of this type was an example of origin of both great vessels from the arterial ventricle in a subject with situs inversus (Fig 8,*b*) and asplenia In this case with mirror-image dextrocardia, there were complex malformations including right (arterial so-called mitral) atrioventricular valvular atresia. In addition there was ventricular inversion and origin of both great vessels from a hypoplastic right-sided (arterial) ventricle The great vessels were transposed and their interrelations were similar to that found in corrected transposition. The pulmonary veins connected in a normal fashion to the right side of the common atrium. The mixed venous and arterial blood then passed through the left-sided atrioventricular valve into a huge left-sided ventricle which was smooth walled and did not possess a crista supraventricularis This is characteristic of the left-sided ventricle when ventricular inversion is associated with mirror image dextrocardia, as noted by Schiebler and associates.[33] The only outlet for this chamber was a ventricular septal defect of the A-V commune type." Both great vessels took origin from the hypoplastic right sided (arterial) ventricle The pulmonary valve was congenitally bicuspid and stenotic. This case was described in detail by Ruttenberg and associates

Associated anomalies in mitral atresia

In addition to the coexistent anomalies upon which the given classification of mitral atresia was based, certain cases showed other coexistent anomalies. Among them, anomalies of the aortic arch occurred frequently in all cases, particularly in Group I. Among the 14 cases with coexistent mitral and aortic atresia (Group I, Type A) the aortic arch was included in 9 of the specimens studied: aortic coarctation occurred in 5 (Fig. 5,*b*) and tubular hypoplasia of the arch in 1. Among the 10 cases with coexistent mitral atresia and a hypoplastic but patent aortic valve (Group I, Type B), aortic coarctation occurred in 3 and tubular hypoplasia of the aortic arch in 4. In Group II the associated anomalies included aortic coarctation (1 case), tubular hypoplasia of the aortic arch (1 case), hypoplasia of the ascending aorta (1 case) and right aortic arch (2 cases).

A persistent left superior vena cava coexisted in 3 cases of Group I and in 5 cases of Group II. Atresia of the right atrial ostium of the coronary sinus occurred in 3 cases of Group I and in 2 of Group II.

In Group I, anomalies of the pulmonary veins were noted in 2 cases of Type A and in 4 cases of Type B. In 4 of these 6 cases this took the form of anomalous pulmonary venous connection. In 1 case the pulmonary venous anomaly was represented by cor triatriatum, and in the last by isolated stenosis of the left lower pulmonary vein. In 3 of these 6 cases, mitral atresia and premature closure of the foramen ovale coexisted. Pulmonary venous obstruction occurred in each of these 6 cases. The pulmonary veins were generally thick walled. Details of pulmonary venous anomalies in mitral atresia are the subject of a report by Shone and Edwards.[33]

Clinical features and comment

The clinical patterns in mitral atresia may be divided into two major groups based upon the same pathologic classification outlined earlier in this report. In general, the heart with mitral atresia should be considered to be essentially a two-chambered organ. Data concerning the sex and age at death in these 32 cases of mitral atresia are given in Table II.

Mitral atresia with great vessels normally

Table II. Sex and age at time of death in 32 cases of mitral atresia

Anatomic type		*Sex*			*Age at death*
Designation	*Number of cases*	*Male*	*Female*	*Not recorded*	*(Number of cases)*
Group I, Type A	14	9	3	2	1 day (5) 2 days (3) 3 days (2) 6 days (1) 10 days (1) 60 days (1) Not recorded (1)
Group I, Type B	10	4	5	1	1-4 days (6) 8 wk. (1) 10 wk. (1) 11 wk. (1) 2 yr. (1)
Group II, Type A	7	7	0	0	1 day (1) 2-3 wk. (2) 2-1½ mo. (3) 15 yr. (1)
Group II, Type B	1	1	0	0	4 yr. (1)

Interrelated and hypoplasia of the left-sided cardiac structures (Group I Types A and B)

VENTRICULAR SEPTUM INTACT Because of their clinical physiologic and radiographic similarities, Type A and Type B without ventricular septal defect will be discussed together Special features of Type B with ventricular septal defect will be discussed separately

In those cases having hypoplastic left sided chambers (Figs. 3 and 6,*a*) pulmonary venous blood enters the right atrium as follows (1) most commonly through a secondary interatrial communication created by herniation and prolapse of the valve of the foramen ovale into the right atrial cavity[4-6,14] (2) also frequently by way of a true atrial septal defect at the fossa ovalis or through a defect of the ostium primum type or (3) by way of anomalous pulmonary venous return to the right atrium In patients having this anomaly the right ventricle must obviously maintain both the pulmonary and the systemic circulations, since the left ventricle is a nonfunctioning chamber Whether the aortic valve is stenotic or atretic is unimportant from the functional standpoint. In either case because the ventricular septum is intact the circulation is as though there were no openings between the left ventricle and the aorta. The mixed pulmonary and systemic venous blood from the right atrium then passes into the right ventricle and is ejected into the enlarged pulmonary trunk. From the pulmonary trunk, blood enters the aorta through a patent ductus arteriosus. Coronary arterial supply is maintained by a retrograde flow of blood through the ascending aorta.[4,7] Essentially then, the ascending aorta acts as a common coronary artery as termed by Neufeld and associates.[14]

Clinically and physiologically these patients resembled those having isolated aortic atresia. Shortly after birth these patients may appear to be normal cyanotic or pale and weak. Those who appear to be normal usually develop dusky cyanosis and respiratory distress within a period of 24 hours after birth In the majority of instances, death occurs within the first 3 days of life (Table II) A nonspecific soft systolic murmur or an apical mid-diastolic rumble represents the major auscultatory finding Specific physical or electrocardiographic findings in this condition are lacking The diagnosis rests upon a high index of suspicion and selective angiographic studies.

The *electrocardiogram* in this type of mitral atresia is similar to that seen in aortic atresia, wherein right axis deviation P pulmonale and right ventricular hypertrophy are common findings (Fig 9)

Roentgenograms of the thorax and a forward angiocardiogram in a 2 month-old male infant with coexistent aortic and mitral atresia were available for review In addition coarctation of the aorta patent ductus arteriosus, and a large atrial septal defect were present The roentgenograms (Fig 10) showed marked cardio-

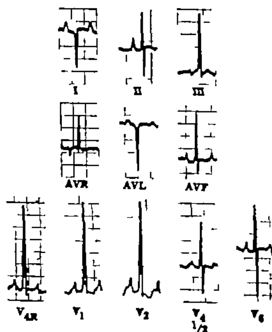


Fig 9 Group I Type A Coexistent mitral and aortic atresia. The standard electrocardiogram reveals marked right axis deviation of the QRS axis in the frontal plane (+140 degrees) The R waves are tall in the right-sided precordial leads (V4R), and correspondingly there are deep S waves in the left-sided precordial leads The P R interval is prolonged being 0 16 second in duration The P waves are peaked in Leads I II and AVF as well as in the right-sided precordial leads (V4R, V1, and V2) This electrocardiogram suggests first degree atrioventricular block, right ventricular hypertrophy and right atrial enlargement.

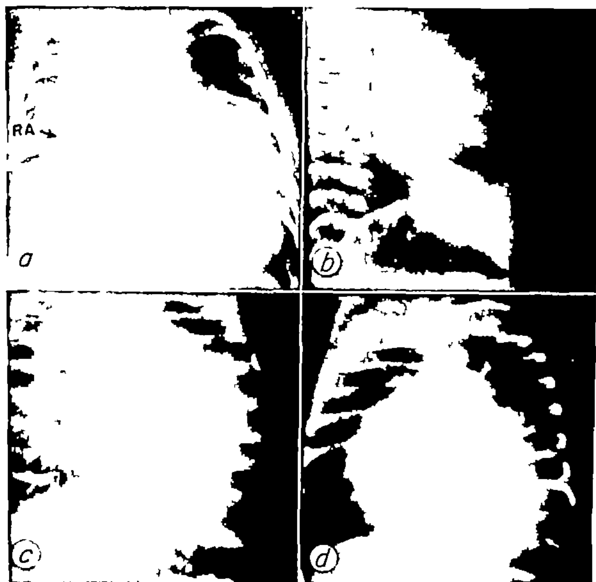


Fig. 10. Roentgenogram of the thorax in a case of [illegible] with [illegible]existent aortic and mitral atresia. Pathologic specimen is shown in Fig. 1,b and 5,b. a, Frontal view showing marked cardiomegaly primarily on the basis of enlargement of the right atrium (*RA*) and right ventricle. b, Lateral view. c, Right anterior oblique view. d, Left anterior oblique view showing prominence of the left-posterior aspect of the heart (*arrow*), which finding is ordinarily on the basis of enlargement of the left side of the heart.

megaly with enlargement of the right atrium and right ventricle. In the left anterior oblique view there was prominence of the left posterior aspect of the heart suggestive of left-sided enlargement but in fact caused by a markedly enlarged right ventricle.

A forward angiocardiogram showed sequential opacification of a strikingly enlarged right atrium, right ventricle, and pulmonary trunk. After this, contrast material appeared in the descending thoracic aorta through a patent ductus arteriosus. Simultaneously, contrast material passed into the left atrium, following which there was reopacification of the right-sided chambers and pulmonary trunk. Contrast material continued to recirculate through the lesser circulation during the remainder of the study.

VENTRICULAR SEPTAL DEFECT. In patient with mitral atresia having hypo-

plastic but patent aortic valves and ventricular septal defect (Fig 4,*a*) mixed pulmonary and systemic venous blood from the right atrium enters the right ventricle Most of it is ejected into the enlarged pulmonary trunk. Some blood will however enter the hypoplastic left ventricle and thence, the aorta

In general the clinical picture is like that in Type A and in Type B without ventricular septal defect. An exception however is the presence of a harsh systolic ejection murmur representing aortic stenosis, which is heard maximally along the left sternal border

Electrocardiograms were available for review in 3 of the 9 cases of Group I Type B having a ventricular septal defect In 2 of these there was right axis deviation and P pulmonale (Fig 11,*a*) The QRS loop in the frontal plane was inscribed in a clockwise direction in 1 case there was a figure-of-eight or propellor-shaped inscription of the QRS loop in the frontal plane (Fig 11,*b*) Precordial leads were obtained in 1 of these 2 cases which demonstrated right ventricular hypertrophy In the third case (an example of common atrium) there was left axis deviation and P mitrale.

A single *thoracic roentgenogram* in this subgroup was available for review This showed cardiomegaly with elevation of the cardiac apex and prominence of the right atrium (Fig 12)

Mitral atresia with great vessels transposed and common ventricle (*Group II Type A*) In these cases (Fig 8,*a*) the mixed pulmonary and systemic venous blood from the right atrium enters a common ventricular chamber The distribution of blood ejected from this common ventricle depends upon the degree of obstruction to flow offered by the pulmonary and aortic channels. In 3 of our cases of this type the pulmonary valve was atretic and both the systemic and pulmonary blood flows were derived from the aorta. In an additional case of this type severe pulmonary stenosis effected a similar distribution of blood

The clinical course in patients having this form of mitral atresia was more variable than that in patients with any other form of mitral atresia Most infants with common ventricle and mitral atresia showed cyanosis of some degree from birth or shortly thereafter It was usually noted first during crying or feeding The most marked degrees of cyanosis, however occur in those patients in whom the pulmonary valve is either atretic or stenotic A systolic murmur is usually heard over the precordium Its location intensity and quality vary however and are dependent upon the coexisting cardiac anomalies. The survival in this group was also more variable than in any of the other forms of

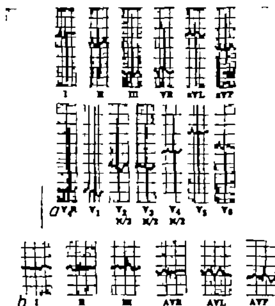


Fig 11 *a* A 11-week-old girl with Group I Type B mitral atresia. The electrocardiogram reveals marked right axis deviation of +130 degrees in the frontal plane The P R interval is 0 16 second The T waves are peaked and prominent in Leads I II and V There are qR complexes in Leads V_4R and V_1, and a deep S wave in Lead V_6. The electrocardiogram is compatible with marked right ventricular hypertrophy and marked right atrial hypertrophy *b* Group I Type B A newborn male infant having a single atrium mitral atresia, both muscular and membranous ventricular septal defects, tubular hypoplasia of the aortic arch, and patent ductus arteriosus. The electrocardiogram reveals sinus rhythm. The electrical axis in the frontal plane is +45 degrees. The QRS complex is prolonged to 0 09 second, indicating some form of intraventricular conduction disturbance Furthermore there is a prolonged P-R interval (0 19 second) representing first-degree heart block. The P waves might suggest biatrial enlargement The divergence between the major QRS axis and the major T vector suggests further the probability of intraventricular conduction disturbance Precordial leads were not available.



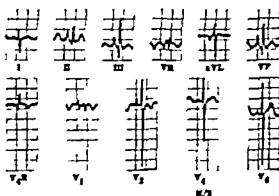
Fig. 12. F tal tgenogr m of thor x showing ardiomeg ly ele tion of cardiac apex, and prominence of right tr m an example of m tral tresia Group I Type B

mitral atresia. Six patients of this group died within 41 months after birth but the remainin ne patient survived to the a e of 15 years. In the latter case no pul monary stenosis was present.

The availa le *electrocardiograms* in the cases of Group II Type A showed right axis deviation of approximately +170 degrees with evidence of right atrial en largement (Fig. 13). In each in the frontal pl ne the QRS loop was inscribed in a clockwise direction. In the right sided precordial leads there was a qR pattern in Lead V . The mid precordial leads (V_1 through V_4) showed an rS pattern. In the left-sided prec rdial leads there were R or rS complexes and no Q waves.

The electrocardiographic range in cases of tran position of the great vessels with common ventricle and with both atrioventricular valves patent includes the patterns found in this condition. The electrocardiographic diagnostic criteria of common ventricle may be of some value here also. Common ventricle is suggested by the presence of (1) stereotyped QRS complexes in the precordial leads (3 cases) and (2) absent Q waves in the "left-sided" precordial lead.

Roentgenograms of the thorax with forward angiocardiographic studies were available for review in 2 patients with mitral *atresia common ventricle inversion of the* infundibulum and obstruction to pul monary flow. In each case frontal roent genograms (Figs. 14 and 15) of the thorax showed marked cardiomegaly and a convex prominence of the upper left cardiac bor



F . 13. A -month-old m le. Group II Type A. The QRS the frontal plane i rightw d with a major QRS xis of +170 degrees. The P w es are pe ked nd promine t Lead II nd III as w ll a n Lead aVF. The precordial lead are stereotyped config t n, being of the rS type ex ept f r Lead V_{4R} wh h shows a qR m. No Q w en seen n the left-sided prec rdial le d. The lectrocard gram is c mpatible with right trial enlargement and mmon ventricle.

der the latter representing the underlying infundibulum The pulmonary vasculature appeared to be attenuated Forward angiocardiography in each of these 2 cases (Figs. 14 and 15) demonstrated sequential opacification of the right atrium common ventricle, inverted infundibulum and an enlarged aorta. In one case with pulmonary stenosis, the pulmonary trunk and aorta opacified simultaneously in the other case associated with pulmonary atresia the pulmonary vasculature opacified *through a patent ductus arteriosus.*

Mitral atresia with great vessels transposed and two ventricles present (Group II Type B) The clinical electrocardiographic and roentgenographic features of the single example of this group (Fig 8,*b*) have been the subject of a previous report[24] and will not be reviewed here The only clinical information from this case which suggested mitral atresia was the high degree of oxygen saturation of the blood in the venous atrium

Discussion

From an anatomic standpoint the most *common form of mitral atresia is that* which is associated with aortic atresia Next most common is the association of

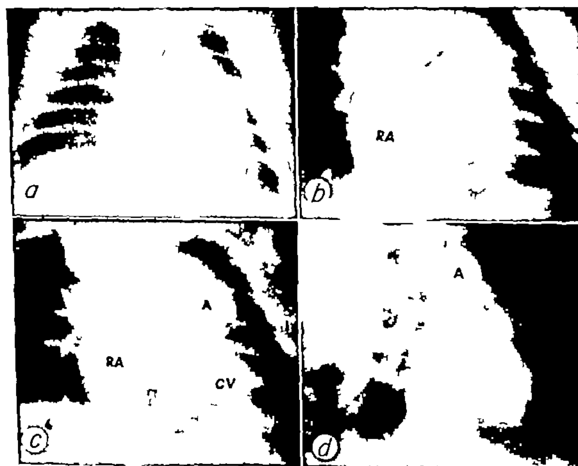


Fig *14* Mitral atresia associated with common ventricle Inversion of infundibulum, pulmonary stenosis and right aortic arch (Group II Type A1). *a*, Frontal roentgenogram of thorax, showing marked cardiomegaly *b c* and *d* Forward angiocardiograms. *b* Frontal view early in study showing an enlarged right atrium (*RA*) *c* and *d* Subsequent films in frontal and lateral views, respectively *showing opacification of the common ventricle* (*CV*), inverted infundibulum (*arrow*), and enlarged aorta (*A*), which descends on the right side The central pulmonary vessels appear attenuated. (Illustrations from L. S. Carey and H D Ruttenberg "Roentgenographic Features of Corrected Transposition and Common Ventricle With Inversion of the Infundibulum," American Journal of Roentgenology 92:652, 1964 Reproduced with permission)

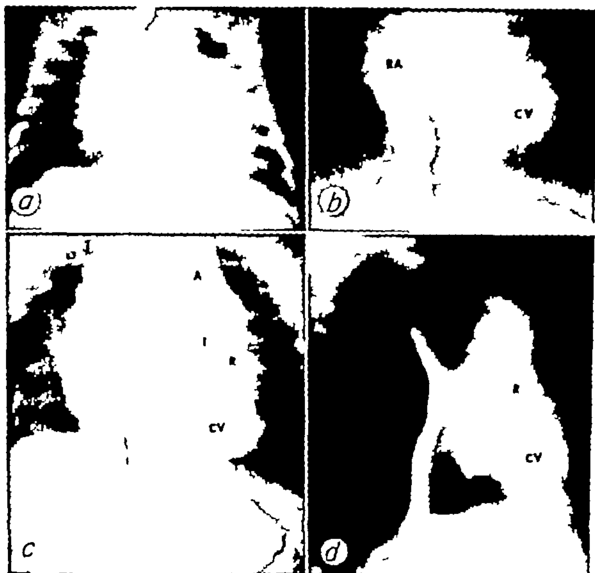


Fig. 15. Mitral atresia associated with common ventricle, inversion of infundibulum and pulmonary atresia (Group I, Type 5). a, Frontal roentgenogram of thorax showing marked cardiomegaly. b, c, and d, Forward angiocardiograms. b, Frontal view early in study showing contrast material streaming through the right A-V valve into the common ventricle (CV). c and d, Subsequent films in frontal and lateral views, respectively, showing opacification of enlarged aorta through the infundibulum (I). R, Infundibular recess. (Illustration from L. S. Carey and R. D. Ruttenberg: Roentgenographic Features of Corrected Transposition and Common Ventricle With Inversion of the Infundibulum. American Journal of Roentgenology 92:652, 1964. Reproduced with permission.)

mitral atresia with a patent but hypoplastic and stenotic aortic valve. Third in *frequency* is the association of common ventricle and transposition of the great vessels with mitral atresia. In only one instance in our experience were two ventricles present when transposition of the great vessels was associated with mitral atresia. Similar findings were described by Sherman.[17] That author, reviewing 11 cases of mitral atresia, found associated aortic atresia in 6, aortic stenosis in 1, and transposition of the great vessels in 4 instances. In all forms the predominant associated anomaly is aortic coarctation or tubular hypoplasia of the aortic arch. The anomalies of the pulmonary veins, as well as a persistent left superior vena

cava were occasionally associated. Pulmonary venous obstruction was found in about one fourth of all cases.

The absence of cardiac murmurs associated with cyanosis may falsely lead one to suspect the respiratory rather than the cardiovascular system until a cardiac murmur or vascular collapse becomes apparent or intervenes. Electrocardiographic and roentgenographic studies are of limited value in the differential diagnosis.

Forward angiography is probably the most useful and least risky diagnostic procedure in mitral atresia. Since the malformation frequently is associated with other complex congenital cardiac anomalies, several different patterns of contrast flow may be seen. When mitral atresia is associated with aortic atresia and a hypoplastic left ventricle (Group I, Type A) the contrast material reaches the systemic circulation from the pulmonary trunk through a large patent ductus arteriosus. The ascending aorta is usually small and becomes opacified in a retrograde fashion.

When mitral atresia is associated with aortic stenosis and a hypoplastic left ventricle (Group I, B) it is usually accompanied by a ventricular septal defect. Under these circumstances, there may be simultaneous opacification of both great vessels. In Group I, one of the striking angiographic findings was the presence of a left-to-right shunt at the atrial level resulting in a continuous reopacification of the right-sided cardiac chambers and of the pulmonary trunk.

When mitral atresia is associated with a common ventricle, infundibular inversion, and pulmonary obstruction (Group II, Type A), the presence of the common chamber and of its infundibulum will usually be readily appreciated. In the presence of pulmonary obstruction, the flow from the common ventricle is primarily into an enlarged aorta through the inverted infundibulum.

In each of these examples, the absence of the mitral valve is presumptive; the most exact way to demonstrate mitral atresia is by the injection of contrast material selectively into the left atrium. In Group I, this resulted in dense and immediate opacification of an enlarged right atrium, followed by opacification of the right ventricle. In Group II, there was sequential opacification of the left atrium, right atrium, and common ventricle. Obviously, in the presence of anomalous pulmonary venous connection or levoatriocardinal vein[21, 22] the pattern of flow described above will not pertain.

The exact demonstration of atresia of the mitral valve, however, is academic when the complex and noncorrectable nature of the associated anomalies are recognized during forward angiocardiography.

Summary

A clinical and pathologic review is made of 32 cases of mitral atresia. Mitral atresia usually coexists with other complex cardiac anomalies including aortic atresia, transposition of the great vessels, common ventricle, pulmonary or subpulmonary stenosis, as well as anomalies of the aortic arch. An anatomic classification of mitral atresia is made on the basis of (1) the interrelation of the great vessels, (2) the anatomic state of the left-sided cardiac structures, and (3) the state of the ventricular septum. Group I consists of those cases in which the great vessels are normally interrelated (24 cases) and in which there is hypoplasia of the left-sided cardiac structures with aortic valvular atresia or hypoplasia. Group II consists of those cases in which there is transposition of the great vessels with a common ventricle or two ventricles present (8 cases). The clinical course is usually shorter in the former than in the latter group.

Selective angiocardiography, particularly from the left atrium, appears to represent a reliable method for the clinical diagnosis of mitral atresia.

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Complete interatrial and intra-atrial block (atrial dissociation)

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Intraventricular conduction defects of varying degrees occur often in clinical practice and are recognized without much difficulty. The state of affairs with atrial conduction disturbances is entirely different. Although the milder degrees of atrial conduction defects, such as the pathologic delay of conduction of the sinus impulse to the left atrium, are well known, higher degrees of atrial blocks, although not so uncommon, are often not diagnosed.

The impulse originating in the sinoatrial node is transmitted via several pathways, first to the right atrium and then to the atrioventricular node and the left atrium. Of the numerous muscular bundles available two are "preferred" by the sinus impulse because they are the shortest from their origin to their destination. These preferential pathways are the interatrial bundle of Bachmann, conducting the impulse from the "head" of the sinus node to the left atrium, and the muscle fibers contained in the Torus Loweri, transmitting the stimulus from the middle or lower, or "tail," part of the sinus node to the A-V node (Rothberger and Scherf).

Older experiments of clamping, ligature or destruction of these transmission routes of the sinus impulse did not take into consideration the importance of the concomitant throttling of the supply of arterial blood to the sinus node and portions of the atrial muscle bundles.

The abundance of such muscular communications made it difficult for many investigators to give credence to situations in which all routes of intra-atrial and interatrial conduction of the sinus impulse are blocked simultaneously. Among such skeptics, Lewis, who hesitated to accept the diagnosis of complete interatrial block in the case reported by Schrumpf, ranked foremost. However, this lesion has been observed by many investigators: by Hering in the dying heart, by Fredericq, and by Erlanger and Blackman in animal experiments. What is more important from a clinical point of view is the fact that these disturbances in atrial conduction were observed in dogs during an insufficient perfusion of the heart without any additional mutilating manipulations (Scherf and Siedeck).

Four clinical instances of this type of block will be discussed in the present report.

Clinical observations

Observation 1. E. T., a 66-year-old woman, was hospitalized in coma due to a cerebral infarct. She was suffering from arterio-

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sclerotic heart disease with congestive heart failure for which she was receiving digitalis. Several electrocardiograms were taken during her stay in the hospital from June 26 to July 12, when she died. A postmortem examination revealed generalized arteriosclerosis, a recent massive cerebral infarct, and an old occlusion of the anterior descending branch of the left coronary artery with a corresponding old infarction of the left ventricle and interventricular septum, mural thrombi in the left ventricle with partial organization, chronic cor pulmonale, pulmonary fibrosis, and thrombosis of the left pulmonary artery.

The electrocardiogram obtained on June 28 (Fig. 1) revealed a completely irregular ventricular activity as encountered in atrial fibrillation. Leads II, III, aVR, aVL, aVF, V_1, V_2, and V_3 are shown. The QRS complexes are slurred, and the T waves in Leads I (not shown), II, V_2, and V_4 (the latter two not shown) were abnormal. Particularly interesting was the atrial electrocardiogram which was most distinct in Leads II, III, and aVF. In these leads, positive, somewhat peaked P waves are seen at a rate of about 58 to 62 per minute. These P waves are followed by a short fibrillatory movement. These microwaves are at first very low and irregular but soon become more regular with a rate of about

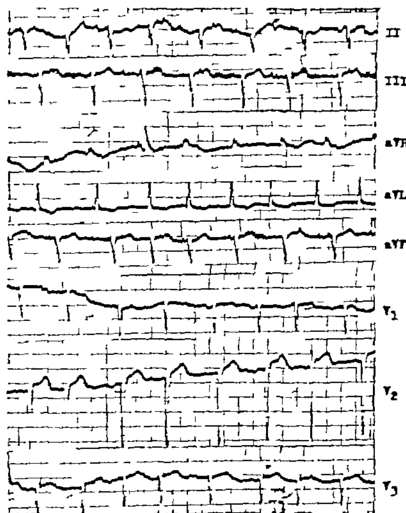


Fig. 1. Observation 1. The ventricular rhythm is irregular and fibrillation waves are seen in Lead V_1. In Leads II, III, and aVF one sees regularly appearing P waves followed by coarse, irregular and then regular small waves representing focal fibrillation lasting 0.60 to 0.70 second.

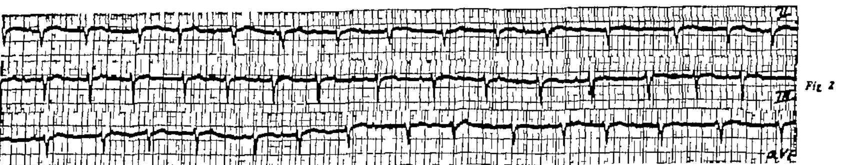


Fig 2 Observation 1 This tracing was obtained 7 days after Fig 1 with a different electrocardiograph In Leads II III and aVF again irregular ventricular activity is observed as in atrial fibrillation no P waves precede the ventricular complexes. Positive P waves are observed regularly with a rate of 52 to 55 and again are followed by the small vibratory movements of the string

Fig 3 Observation 1 These two groups of three tracings were obtained 3 and 4 days, respectively after those of Fig 2 These tracings permit again the diagnosis of atrial fibrillation in the presence of regularly appearing P waves followed by focal fibrillation

1,500 per minute These oscillations are also present although less clearly visualized in Leads aVR V_1 and V_2 (and in V_3)

As soon as this disturbance was recognized *another tracing was taken from the* patient with another electrocardiograph (Fig 2 obtained on July 5) Leads II III and aVF are reproduced These strips show the same irregularity of the ventricular activity and again regular positive P waves this time at a rate of 52 to 55 per minute Again *the fine at first irregular and low then regular rapid and small* vibrations following the P waves are observed In addition in diastole low waves are seen as in fibrillation in Leads III and aVF however artifacts could not be excluded

Strips of two more tracings of this patient are presented in Fig 3 They were obtained on July 8 (the upper three strips of Fig 3) and on July 9 (the lower three strips of Fig 3) On July 8 Leads II aVF and V depict in principle the same disturbance The atrial rate varies between 47 and 54 per minute the small vibrations are less regular than those shown in Figs 1 and 2 but here also they distinctly follow each P wave and last as in the previous tracings, about 0 60 second In these tracings again in diastole small waves are seen identified in Lead V_1 as being *due to impure flutter or coarse* fibrillation

Leads II aVL and V_6 taken July 9 (the lower three strips of Fig 3) show the same irregularity of the ventricles. The P wave whose rate best calculated in Lead II fell to about 33 to 37 per minute is followed by *microfibrillation. In addition the impure flutter or coarse fibrillation* waves are again present

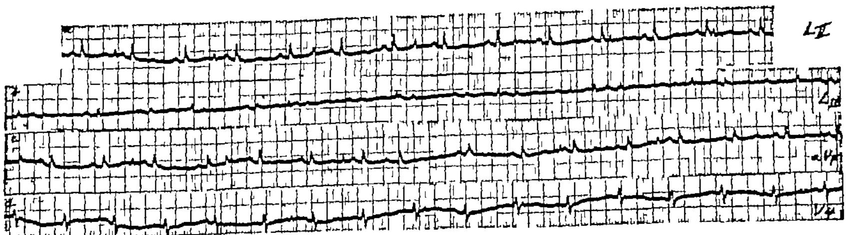
On the basis of these tracings, taken with four different electrocardiographs and by different technicians, we must assume that one atrium or part of one atrium revealed impure flutter or coarse fibrillation whereas the other *atrium or the bulk of the atrial* muscle mass was activated separately and independently showing regularly occurring P waves at rates that became progressively lower during the period of observation In addition there was evidence of focal localized, or "partial fibrillation following and probably initiated by the preceding f waves

It is impossible to identify precisely the areas in the atrial muscle which are responsible for the *multicentric activity of the upper chambers of the heart*

Against artifacts which may reasonably be suggested by the great regularity of the small waves following the P waves in Fig 1 speak the following facts (1) the registration of the same arrhythmia *with different electrocardiographs and by different technicians (2) the absence of this abnormality in other patients on the* days these tracings were taken (about 30 additional tracings were obtained daily by four technicians) (3) the presence of this disturbance during 11 days, whenever electrocardiograms were *obtained from* this patient and (4) the typical pattern which fits the following observations and those reported in the literature

Observation 2 M B a 65-year-old woman was admitted to hospital in congestive heart failure and with marked *anemia (her hemoglobin on admission was 4 7 Gm per 100 c.c of blood)* Three days after admission the patient died

The upper two strips of Fig 4 show Leads II and III obtained on the day of admission whereas the lower two strips depict Leads aVF and V_4 and were taken *2 days later In all tracings there is a regular sinus rhythm with normal P waves* at a rate fluctuating between 88 and 93 per minute and a P R interval measuring 0 18 second The T waves appear to be abnormally low and the QRS complexes reveal a low voltage. In addition there is in all leads another group of P waves these appear *rather regularly at a rate of 46 to 47 per minute in the upper two strips of Fig 4 (a and b)* but are irregular in rhythm in the lower two tracings (*c* and *d*) with rates fluctuating between 28 and 48 per minute. The successive intervals between the second set of P waves in Fig 4,*c* in hundredths of a second are as follows 148 124 154 160 120 126 and 210 *The same intervals in Lead V_4 (Fig 4,d) are 140 112 172 124 260 and 172* The superadded P waves are narrower and more peaked than the sinus P waves. Here again the ectopic P waves are followed by small vibrations, being particularly clear



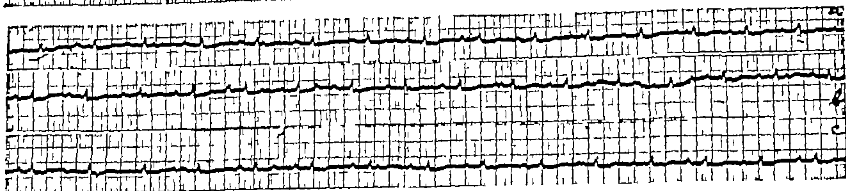


Fig 4 Observation 2 The upper two tracings are Leads II and III the lower two tracings obtained with a different apparatus, are Leads aVF and V taken, 2 days later The tracings show a regular sinus rhythm with a P R interval of 0 18 second An atrial extrasystole appears in Lead aVF In addition independent positive P waves are seen with a slow rate rhythmic in the upper two strips, irregular in the lower two strips. Here again these P waves are followed by the small waves representing fibrillation of part of one atrium or of one whole atrium.

Fig 5 Observation 3 The three tracings represent Lead II taken on three different occasions within 11 days. In all tracings a sinus rhythm is present with a P R interval of 0 4 second Another set of independent P waves with a rate of about 40 is seen followed by the fine vibrations. The latter last about 0.60 second

of one atrium then this occurrence represents a form of complete intra atrial block.

The interatrial block is classified as either a partial (or incomplete) block or a complete one. A partial interatrial block exists when there is a delay in transmission of the impulse from one atrium to the other or theoretically when some impulses are not conducted from the right to the left atrium. (This has been demonstrated experimentally in rabbits by Erlanger and Blackman who have used the term partial auriculo-auricular block and in chickens by Zuckermann and associates.) When the solidarity and harmony which normally exist between the two atria are completely abolished we speak of complete interatrial block. In such a condition each atrium is activated by its own pacemaker independently of the other.

Several terms have been used to identify the latter disturbance namely intra auricular dissociation (Lewis) inter auricular dissociation (Moreira Mahaim Lian and Golblin) atrial dissociation with double atrial pacemaker double atrial rhythm (Lian and Golblin) atrial dissociation (Deitz and associates) and total atrial dissociation (Latour and Puech). Geraudel[3] used the picturesque term la double commande for several arrhythmias in which two associated but independent rhythms exist. The arrhythmia under discussion in this article falls, according to Géraudel into the category of double commande auriculaire.

Often it is not possible to differentiate the interatrial from the intra atrial block because a definite localization of the site of the block cannot be made. It seems to be a fact that a normal or almost normal P wave can be formed by the activity of one atrium alone or even by the activity of a portion of the atrial musculature.

The appearance of localized fibrillation lasting less than a second after each abnormal P wave in our cases demonstrates in our opinion that we are dealing with a factual phenomenon and not with artifacts.

The exclusion of artifacts before the diagnosis of complete interatrial block is accepted is of paramount importance. A loose electrical contact particularly of electrodes, the abnormal heartbeats of another person who happens to touch the patient a rhythmic tick or contraction of the diaphragm as in hiccough[4] or diaphragmatic flutter or rhythmic movement of other somatic muscles may cause such artifacts. Renschler and Hanim succeeded in inducing rhythmic contractions of the muscles of the forearm and of the pectoral muscle which simulated the P waves of the electrocardiogram. Interference from a dial telephone electric saw or buzzer or the placing of the hand on the electrodes (Katz) may also be responsible for vibrations which mimic P waves.

All degrees of intra-atrial and interatrial blocks have been produced experimentally. Hering described complete interatrial block of the dying mammalian heart when he observed waves that were slowly propagating over the atria stop on their way. Complete interatrial block has been obtained by Fredericq by Erlanger and Blackman by Condorelli by Scherf and Siedeck, and by Zuckermann and associates. Drury[5] induced varying degrees of both intra atrial and interatrial blocks in the dog by applying different degrees of pressure on or by cooling of the atrial musculature. Frau and Agostoni[6] were able to interfere with the diffusion of the impulse in one atrium or between the atria by infiltrating quinidine or by clamping the atrial wall.

Uniatrial ectopic rhythms such as a uniatrial flutter and fibrillation have appeared experimentally in the hearts of animals in the agonal state, or when poisoned or made anoxic (Condorelli Zuckermann and associates). Scherf and Siedeck have produced interatrial conduction disturbances by ligating muscle bundles of the atria. The rhythms produced were due to independent activity of both atria a slow regular rhythm of the right atrium under probable control of the A V node with normal beating of the left atrium probably activated by the sinus node or the reverse, namely sinus control of the right atrium and probable A V dominance of the slower left atrium or even fibrillation of the right atrium with the left one beating forcibly but irregularly. Extrasystoles confined to only one atrium have been reported experimentally (Kisch Scherf and Siedeck).

Sharma[7] has produced in dogs by the

topical application of acetylcholine or methacholine coupled with brief atrial stimulation at a high rate fibrillation confined to the treated portion of the atrium while elsewhere the atria revealed atrial flutter or sinus rhythm

A recent survey of the clinical literature on the subject under discussion including a report of 8 cases of our own was published by us.[1] References not mentioned in this article may be found in the authors monograph.[1] Here we intend to add a few additional references.

Rautenberg[8] using simultaneously the jugular venous pulse and a pulsation registered from the esophagus, described one observation of "paralysis" of the left atrium (fibrillation?) and a regular slow rhythm of the right atrium

Faber[9] described 2 cases (without presenting tracings in his article although such tracings, obtained with needle electrodes from the chest were presented at the 15th Scandinavian Congress of Internal Medicine 1931) The first case of Faber was that of a 75 year-old man who presented two sets of P waves positive P waves followed by ventricular response at a rate of about 59 per minute and P waves which were inverted (not mentioned in what leads) at a rate of 83 per minute. The second case was that of a 62 year-old woman with a blood pressure of 170/100 mm Hg She was receiving digitalis. The tracing showed a normal P wave at a rate of 80 per minute controlling the ventricles and a second independent group of P waves at a rate of about 97 per minute

Rubino[10] reported on a 41 year-old patient with mediastinopericarditis who had a prolonged atrioventricular conduction time Ocular pressure brought about an A V and an interatrial block. The left atrium was studied with an esophageal lead while the right one was investigated simultaneously with a special (mouth xiphoid process) lead. Originally the case showed a delay of propagation of the impulse to the left atrium during ocular pressure the esophageal lead did not reveal any response of the left atrium whereas the special lead registering the activity of the right atrium continued to demonstrate sinus P waves

Wenger[4] reported a case which demonstrated flutter of the right atrium discovered with intracardiac leads and fibrillation of the left atrium observed with a simultaneous esophageal lead

Marques[11] reported 3 additional instances of total interatrial block. The published tracings are rather poor in so far as technical details are concerned but from the description there is no doubt that these 3 cases correspond to the double P variety of complete interatrial block with localized atrial fibrillation following the ectopic beat. The first instance was in a 52 year-old male patient with chronic bronchitis the rate of the sinus rhythm was 56 per minute the ectopic P waves had a rate of 25 to 40 per minute and were followed by microfibrillatory oscillations. The second case was that of a 56-year-old male patient with myocardial infarction which led to congestive heart failure The electrocardiogram revealed sinus P waves at a rate of 112 per minute, whereas the ectopic P waves had a rate of only 23 per minute and were followed by microfibrillation The third of Marques patients was a woman suffering from recurrent bronchitis and nocturnal paroxysmal dyspnea. The rate of the sinus P waves was 70 per minute but that of the superadded P waves was not given in the article the ectopic P waves again were followed by localized microfibrillation

Masoni and associates[12] registered electrocardiographic, phonocardiographic and intracardiac pressure tracings (the latter taken through a cardiac catheter) in a patient reported on in one of their previous publications dealing with the subject under discussion The electrocardiogram revealed the double atrial rhythm as two sets of independent P waves The interesting part of that investigation was that the respective tracings showed also phonocardiographic and manometric expressions of the ectopic P waves. In the same article, the authors gave a short description of another observation of the same arrhythmia the case was that of a 61 year-old male patient with hypertension emphysema and bouts of bronchitis. The ectopic P wave was positive in Leads II III and aVL and negative in Lead V_1. Its rate was about 26 per minute

An instance of atrial dissociation has been recently reported by Hayes and

Kerby.[14] It concerned a 75-year-old Negro man who suffered from congestive heart failure which led rapidly to his death. In the tracings of this observation there were two sets of P waves: some of the P waves were conducted to the ventricles at a rate of 130 per minute, whereas the ectopic P waves were not conducted and had a rate of 75 per minute. Another tracing of the same patient, taken a few hours after the first, revealed a merger ("fusion") of the two kinds of the P waves into a single but notched wave, signifying some degree of an interatrial or intra-atrial block.

Mechanism of production of complete interatrial and intra-atrial block. The mechanism of these atrial conduction disturbance in man is not known. Unconfirmed theories have been expressed in the past, and the findings of several investigators, especially of the Italian School, concerning partition of the sinus node have also not been confirmed. The appearance of atrial block in experiments after ligation of certain muscle bundles or of certain branches of the coronary system or in experiments with insufficient perfusion of the heart may hint at the mechanism of these atrial conduction defects. Several of our patients had an inferior (diaphragmatic) myocardial infarction due to a lesion in the right coronary artery, which, in most human hearts, supplies branches to the sinus node, A-V node, and the upper portion of the A-V conduction system. Some patients had bronchogenic carcinoma which may have invaded the atria and consequently may have interfered with the normal transmission of the sinus impulse. There have been very few anatomic investigations of patients who during life had electrocardiograms which showed a complete block between the atria. In one such case a primary reticulum cell sarcoma of the heart with extensive infiltration of the atrial walls was found at autopsy (Lenègre and associates). In one recently published observation of markedly widened double-peaked P wave, a severe coronary sclerosis with "focal" fibrosis of the bundle of Bachmann was found.[15]

It has been proved that the formation of impulses may occasionally take place in the left atrium.[16] Such formation of impulses is certainly common in the area of the A-V node. A more precise localization of the region initiating the ectopic P wave in those cases in which two independent atrial rhythms coexist, with positive P waves in Leads II and III, is not possible. In not one of the four observations reported here were there inverted P waves in Lead I; such an occurrence would be expected with the formation of impulses in the left atrium. However, in all four instances the superadded P waves were poorly visualized in Lead I.

Marques[12] expressed the opinion that the additional ectopic P waves and the following microfibrillation are extracardiac in origin and that they are related to the respiratory phases, since the P waves coincide with the beginning of inspiration and the following microfibrillatory vibrations are produced during the inspiratory phase. This theory explains, according to Marques, the fact that this variety of interatrial block often occurs in patients with chronic bronchitis and pulmonary emphysema. The author cautiously adds that other factors may play a role in the production of this phenomenon.

The appearance of atrial fibrillation after every atrial impulse has been observed experimentally, particularly during vagal stimulation or under the influence of acetylcholine.

Incidence. Complete interatrial block is not so rare a phenomenon as one is given to believe. When in our service the interest in this disturbance was heightened, we were able to uncover 9 cases in as short a time as 8 months. It seems that the Biblical dictum, "seek and ye shall find," is here fully applicable.

Etiology. Complete interatrial block has been reported during attacks of rheumatic fever (Bay and Adams), during myocardial infarction, especially in its inferior (diaphragmatic) localization, during digitalis intoxication (Schrumpf, Deitz and associates), during a uremic crisis (Bay and Adams), in the presence of coronary sclerosis (Lian and Golblin, Scherf and Cohen), in severe cardiopathies of any kind, especially before death, during diphtherial "myocarditis" (P. Giraud and associates), in cancer of the lung (Igarashi and associates), and in primary sarcoma of the heart (Lenègre and associates).

Prognosis. In general the prognosis in these cases is extremely poor; the patients usually die within days or weeks after the appearance of this disturbance.

The combination of two independent P waves is usually a transient phenomenon. It is supposed to have lasted seconds in one case (Renschler and Ham). Some cases have been reported in which the arrhythmia lasted more than 2 months (Igarashi and associates), a year (Farinelly and associates), 2 years (Masoni and associates), and 3 years (Igarashi and associates). The patients whom we have observed died within days or within a few weeks after the interatrial block was discovered (except for one patient who left the hospital in a poor condition and who was not followed up). It is probable that instances of complete interatrial block will be observed in which such a gloomy prognosis will not be justified. Interatrial block may perhaps occur as the result of a purely atrial lesion, when a segmental type of atherosclerosis involves only the arterial supply of the atria.

Diagnosis and differential diagnosis. Total, complete dissociation between the atria is diagnosed when two sets of P waves of different shape exist, when these two groups of P waves are independent of each other, or when an ectopic rhythm (fibrillation or flutter) is limited to an atrium (usually the left one) or part of one atrium while the other (usually the right) atrium is under the control of the sinus node. Occasionally, two independent ectopic pacemakers dominate the two atria.

In general, the rates of the two kinds of P waves are different; one P wave may be regular in rhythm, whereas the other may be arrhythmic. Usually, the sinus P wave has a more rapid rate than the ectopic one. Rarely does the ectopic P wave have a rate higher than that of the nomotopic P wave (case of Schrumpf; Case 1 of Bay and Adams). The more rapid series of P waves "floats" around the slower series.

Special elective atrial leads, esophageal leads, and intracardiac leads have assisted in the diagnosis of cases in which intra-atrial block was not suspected on the basis of the 12-lead electrocardiogram. Unfortunately, some of these special procedures could not be used in our patients who were gravely ill.

The differential diagnosis between atrial or A-V nodal parasystole and complete interatrial block by means of the electrocardiogram is not always easy, although the mechanisms involved are different. If one protected center in the atria or A-V node forms impulses independently of the sinus node and each impulse appearing outside the refractory phase spreads over both atria, the same electrocardiographic pattern of the double-P wave variety of interatrial block will be found. To our knowledge, the best differential diagnostic sign is the fact that in interatrial block only one set of P waves is conducted to the ventricle (unless there is a concomitant complete atrioventricular block which stops the propagation to the ventricle of any atrial complex), whereas in supraventricular parasystole every impulse of either center is conducted, provided that it is not blocked by the refractory phase of the A-V conduction system. Occasional reports have been published which purport to show that each of the two P waves in complete interatrial block, having been conducted, elicits its own ventricular response, supposedly by activating different portions of the ventricles. Such conclusions are erroneous and obviously represent artifacts.

Summary

Certain aspects of complete interatrial and intra-atrial blocks have been discussed and four personal, not previously reported observations of this disturbance have been added. A few additional cases scattered in the literature have been mentioned, thus supplementing the extensive review of the subject undertaken elsewhere.

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A simple bedside method for transvenous intracardiac pacing

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It is now generally appreciated that in advanced atrioventricular block when Adams-Stokes attacks are not controlled by drug therapy, transvenous cardiac pacing may be life saving. Humphries[1] points out the usefulness of temporary cardiac pacing for the management of transient conduction disturbance or for the evaluation and treatment of patients under consideration for permanent pacemaker implantation. Also the danger of ventricular asystole or tachycardia that might develop during the induction of anesthesia in patients with heart block may be effectively avoided by temporary catheter pacing initiated preoperatively.

At the present time the most commonly used intracardiac pacing catheter is the bipolar type, although the unipolar electrode catheter is preferred by some authors.[3] During the short time in which these devices have been available they have been shown to be reasonably safe and effective. Nevertheless, the semirigid cardiac catheter electrode requires careful placement and positioning under fluoroscopic control. Also, in our experience, pacing of the heart may be intermittent because of variable contact of the electrode tip with the ventricular endocardium. Since movement to a fluoroscopy room is not always practical and indeed may constitute a real hazard to a critically ill patient who needs oxygen, intravenous drugs, and constant monitoring of vital signs, a technique allowing safe bedside placement of an intracardiac electrode would be of definite value. Such a technique would also increase the usefulness of transvenous pacing in hospitals in which fluoroscopic units are not available 24 hours daily.

Recently a simple technique for identifying atrial activity in complex arrhythmias in which P waves could not be identified in standard electrocardiographic leads was reported.[4] The method utilized a Teflon-coated braided stainless steel platinum-tipped wire advanced via a median arm vein into the right atrium. The platinum tip acts as a sensing electrode, and an intracardiac electrogram is recorded from the distal bare end of the wire. The reported success and ease in using this technique has encouraged us to use it similarly in analyzing complex arrhythmias. In addition, we have modified the technique for pacing the heart after the electrode

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Fig. 1. Apparatus utilized for bedside transvenous intracardiac pacing. The wire suture which acts as the indifferent electrode and the endocardial lead wire for recording electrograms and pacing are shown attached to the battery powered pacemaker. To the left are shown the Rochester and B-D Koehn plastic cannula type of needles used for percutaneous insertion of the pacing wire into a vein.

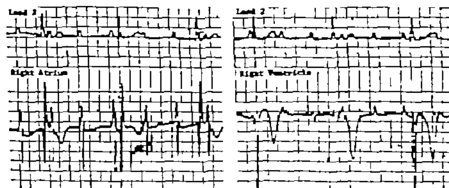


Fig. 2. Simultaneous dual-channel recording of standard limb lead and intracardiac electrograms. Direct right atrial lead is characterized by large biphasic P waves often of greater amplitude than QRS complexes. Deep QS and small P are recorded from the right ventricular endocardium. Tracing retouched for clarity.

fully treated with closed-chest massage during intravenous angiocardiography. The post-resuscitation cardiac rhythm was atrial fibrillation with a ventricular rate of 36 to 40 and frequent ventricular escape beats. Intravenous atropine only temporarily increased the ventricular rate and after several hours the bradycardia became refractory to repeated doses of the drug. Because of the uncertain cardiac status it was desirable to be able to increase the ventricular rate should hypotension or ectopic rhythms develop. The Teflon-coated wire electrode was passed into the right ventricle and after a brief period of trial pacing the unit was turned off and the patient observed continuously. Withholding digitalis resulted in an increased ventricular rate and the wire electrodes were withdrawn after 48 hours.

Case 3. L. I., a 70-year-old hypertensive man with complete A-V block, Adams-Stokes syncope, and heart failure was admitted for evaluation. Careful digitalization and the administration of diuretics and long-acting isoproterenol were unsuccessful in significantly speeding the ventricular rate or controlling the congestive failure. Continuous pacing of the heart at a ventricular rate of 75 per minute with the wire electrode inserted into the right ventricle was associated with a prompt diuresis and a fall in the elevated blood urea nitrogen content to near normal levels. Surgical implantation of an artificial pacemaker was uneventful. The right ventricular intracardiac electrode was withdrawn in the recovery room after having been in place for 5 days.

Case 4. N. N., a very obese diabetic hypertensive 70-year-old woman with a 5 year history of complete A-V block, exertional angina, and severe progressive congestive heart failure was admitted for therapy. Long-acting isoproterenol was given because of persistent episodes of postural hypotension with lightheadedness and nausea. The ventricular rate increased from 45 to 55 per minute. Because the patient failed to show symptomatic improvement on drug therapy the wire electrode was passed into the right ventricle. Pacing at 70 and later at 85 beats per minute did not control the symptoms of postural hypotension or improve the chronic heart failure however. Indicator-dilution studies performed at ventricular rates varying from 45 to 100 per minute failed to demonstrate a significant change in cardiac output with change in rate. The patient was deemed to be an unsuitable candidate for permanent pacemaker implantation. The pacemaker electrode was removed after having been in place for 20 days without complication.

Comment

It is not the purpose of this report to discuss the treatment of complete A-V block or indications for temporary intracardiac pacing. These subjects have been reviewed in several recent and detailed articles.[1,2,4] We are presenting what we believe is a simple, safe, and effective method for interim intracardiac pacing. The technique is easy to master, may be applied quickly, does not require the use of special equipment other than the artificial pacemaker and Teflon-coated electrode, and can be carried out in any situation in which it is possible to perform a venipuncture or cutdown on a vein.

There have been no complications. Neither infection nor clot formation has occurred. Occasionally it has been necessary to abduct or adduct the arm in order to pass the wire through the veins at the shoulder joint. Initially we used a thin-walled 18-gauge needle for the venipuncture and venous cannulation. However, the sharp beveled end of the needle stripped short pieces of Teflon from the electrode on several occasions and conceivably could have cut through the wire completely. We have resolved this hazard by using a type of needle in which a polyethylene cannula is threaded into the vein over the venipuncture needle while the latter is withdrawn from the vessel entirely.

A definite advantage of the wire as a pacing electrode is its flexibility. It is impossible to perforate a vein or the heart. The wire is so flexible it literally floats into the heart. The stiffness of the cardiac catheter type of electrode is a potential hazard even when the catheter electrode is positioned under fluoroscopic control. We have recently had the disturbing experience of finding the tip of a bipolar catheter electrode protruding through the right ventricle and plainly visible to the surgeon when the pericardium was opened during thoracotomy for pacemaker implantation. The catheter electrode had been carefully placed under fluoroscopic control several days before. Protrusion through the heart could not occur with the Teflon-coated electrode.

We have not experienced any difficulties in successfully removing the wire electrode from the right ventricle. Somewhat similar techniques for pacemaking via long plastic-coated wires advanced transvenously into the heart have been reported by others.[3] Vogel and associates[4] speculated that the accidental passage of the wire through the tricuspid valve might result in its becoming tangled around the papillary muscles or chordae tendineae or that a knot might form. Only a greater experience with right

ventricular pacing via the wire electrode will allow us to confidently state whether this is more than a theoretical hazard. At the present time we believe that the simplicity which this technique offers for intracardiac pacing definitely outweighs this theoretical and as yet unreported complication.

Summary

A simple and effective method for transvenous intracardiac pacing is presented utilizing a flexible platinum tipped Teflon coated braided stainless steel wire electrode inserted percutaneously. The advantages of the technique over those using the semirigid cardiac catheter electrodes are discussed. The technique permits intracardiac electrode placement without the necessity of fluoroscopic control and avoids the hazard of cardiac perforation. The procedure may be applied at the bedside with ease and speed even in the most urgent clinical situation.

Several cases in which this method of intracardiac pacing has been successfully employed are outlined and the absence of complications to date is stressed.

Addendum

Since this article was submitted for publication personal experience with the technique has been extended to more than 50 patients. In approximately 20 per cent technical difficulties have been encountered in either passing the wire into the heart or consistently effecting ventricular capture by the battery pacemaker. Occasionally the flexibility of the wire limits attempts to maneuver through the veins, or from right atrium to ventricle. No clots or infection have been encountered.

Formation of a knot has occurred in 4 patients. When the catheter was withdrawn resistance was encountered terminally, the patient complained of mild discomfort in the arm and a small dimple appeared along the course of the vein 4 to 8 cm. proximal to the site of puncture. The knot has been easily extracted through a small incision directly over the dimple.

An article describing a similar technique has also appeared.[9]

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Familial cardiomyopathy

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In 1949 Evans[1] reported on a number of patients with a familial incidence of cardiomyopathy with sudden death and cardiac arrhythmias as particularly prominent features. In reports of familial cardiomegaly or familial cardiomyopathy appearing since 1949[2-20] only a few have presented data on more than two or three patients involving more than two generations.[19,20,21]

We wish to report on a family in which two branches and two generations have been seen personally. Further information about other members in preceding generations and one autopsied case have been obtained.

Case I. J.P. a 27 year-old married white male had noted easy fatigability as a youngster but was active and participated in intramural sports. When he was 17 years old a chest x-ray film recorded by a mobile chest x-ray unit showed an abnormal cardiac silhouette. He consulted a physician who first told him of a heart murmur. His brother Robert P. was also told of a heart murmur at this time and suddenly died shortly thereafter (see Case VII). Although J.P. tires a bit more readily than his friends after strenuous exertion he has led a normal life. He is the father of four children, two of whom have been evaluated by us.

Physical examination on July 2 1958 showed him to be well developed and well nourished with good color. Height feet 7 inches. Weight, 143 pounds. Blood pr 101/60 mm. Hg. Pulse rate 72 per minute and regular. Arterial pulses and jugular venous pulse were normal. No thrills or murmurs were noted in the neck. The precordium was quiet. No thrills or shocks were noted. A Grade 2/6, scratchy systolic murmur was loudest over the second left intercostal space at the sternal border. S_2 at the pulmonary area was normal. Aside from a slightly decreased first mitral sound no abnormality was noted at the apex.

An electrocardiogram (Fig. 1) showed a normal sinus rhythm and left ventricular hypertrophy with ST-T wave changes. Fluoroscopy showed definite cardiomegaly mainly left ventricular enlargement with slight left atrial enlargement as well. The aorta nd main pulmonary artery were normal in size and activity.

He was seen again on Dec. 30 1963. He had noted little change in symptoms. Physical examination now showed prominent third heart sound but was otherwise unchanged. The electrocardiogram (Fig. 1) showed a marked change, however with the development of an intraventricular conduction defect of the RBBB type. An x-ray film (Fig. 1) showed cardiomegaly due to an enlarged left ventricle.

Case II. P.P. 3½ year old girl, the youngest child of J.P. was seen on Dec. 30 1963 because of a heart murmur that had been heard on a routine examination a few months previously. She had no cardiac symptoms and no limitation of her physical activity. She was born 6 weeks prematurely when her mother had pneumonia. She was hospitalized for pneumonia at 7 weeks of age and for gastroenteritis at 1 year of age. She has had frequent chest colds."

Physical examination showed a well-developed nd well-nourished girl with no evidence of cyanosis. All pulses were full and regular and there was no

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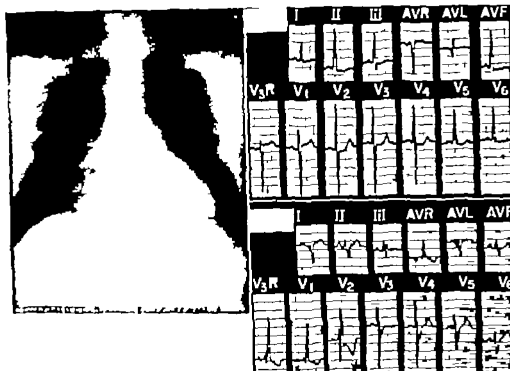


Fig 1 Case I J P (#207471). X-ray film recorded at age 28. Upper ECG obtained on July 2, 1958 age 23. Lower ECG obtained on Dec. 30, 1963 age 28. Leads V nd V of the lower ECG ha e been half standardized.

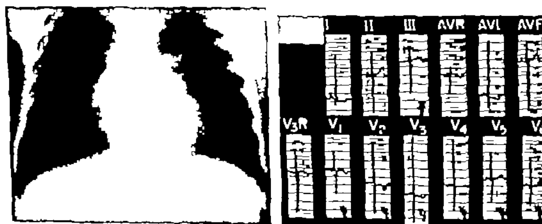


Fig 2. Case II P.P (#207462) 3½-year-old female. ECG recorded on Dec. 30 1963 Leads III and V are half standardized.

femoral leg A systolic thrust was felt at the pulmonary area but pical activity was normal. A low-pitched, ejection type Grade 2/6 systolic murmur was loudest at the aortic area, but was also heard down the left sternal border S_2 at the pulmonary area was normally split. At the apex, S_1 was followed by a late systolic murmur and S_3 by a prominent third heart sound.

An x-ray film (Fig 2) and fluoroscopy showed suggestiv fullness in the area of left entricle but no definite cardiomegaly The electrocardiogram (Fig 2) showed left axis deviation greater than −30 degrees and left ventricular hypertrophy with ST T-wa e changes.

Case III C.P., 7 year old boy of J.P., was seen on Dec. 20 1963



Fig. 3. Case III. C. P. (#207461). 7-year-old male. ECG recorded on Dec. 30, 1963.

murmur that had first been heard 1 year previously. He had been entirely asymptomatic and had no limitation of physical activity. His birth and development had been normal.

Physical examination showed a well-developed and well-nourished boy. Blood pressure 88/60. Pulse rate, 80 per minute and regular. There were no cyanosis, and the arterial and jugular venous pulses were normal. There was perhaps some slight increase in apical activity, but no cardiomegaly was noted. The first and second heart sounds were normal. A faint systolic murmur was present at the aortic area.

The electrocardiogram (Fig. 3) was at the upper limits of normal voltage suggesting left ventricular hypertrophy. An x-ray film (Fig. 3) and fluoroscopy showed no cardiomegaly. The evaluation suggested the possibility of heart disease, but this was not clear cut.

Case IV. Ronald P., a 20-year-old married white male, younger brother of J. P., had been found to have a heart murmur at age 11. The examination was precipitated by the sudden death of his brother Robert P. (Case VII). At age 12, Ronald first noted some fatigue on exertion. At age 14, he was evaluated at another hospital in Denver, and a right heart catheterization was performed (Fig. 4, Table I). Aside from revealing a borderline elevation of the wedge pressure, the catheterization data were normal. At age 15, he began to have some fainting spells on exertion, and these have continued to the present time.

When seen on Jan. 20, 1964, he described dyspnea after climbing three or four flights of stairs, and increased fatigability after such activities as swimming. He usually has a premonition of fainting and avoids an actual loss of consciousness by stopping his activity to rest. If he exerts himself after eating, his dyspnea occurs with much less exertion, and he also experiences a feeling of oppression in his anterior chest. He described one episode of transient rapid heartbeat in the past.

Physical examination showed a stocky, healthy looking young man. Pulse rate, 60 per minute and regular. Blood pressure 120/60 mm. Hg. The arterial and jugular venous pulses were all normal. There was no thrill over the carotid arteries. The precordium was quiet. A slight thrust and possibly a faint thrill were felt over the upper left sternal border. At the aortic area a harsh obstructive systolic murmur was heard. S_2 was normal. The murmur was maximal at the second left intercostal space, where it was Grade 3/6 and was well transmitted diagonally to the apex. S_2 at the pulmonary area was normal. At the apex the first and second heart sounds were normal, and a prominent third heart sound was heard in addition to the murmur.

The electrocardiogram (Fig. 4) showed left ventricular hypertrophy with ST-T-wave changes and probable right ventricular hypertrophy as well. The x-ray film (Fig. 4) and fluoroscopy showed cardiomegaly, mainly left ventricular. Cardiac pulsations were small.

With the clinical impression of diffuse muscular subaortic obstruction and possible right ventricular infundibular obstruction, he underwent right and retrograde left heart catheterization on June 16, 1964 (Table I, Fig. 5). Mild gradients of 10 mm. across the infundibulum of the right ventricle and 10 to 15 mm. across the outflow area of the left ventricle were found at rest. The wedge pressure was elevated, and the cardiac output was normal. Aortic pressure tracings showed the typical contour and the typical lower systolic and pulse pressures of the post premature beat that have been well described in muscular subaortic obstruction.[19] End-diastolic pressures were increased in both ventricles. Pullback tracings were attempted during the administration of isoproterenol. The left heart tracing was unsatisfactory because the catheter could not be manipulated back into the body of the left ventricle. The infundibular gradient showed no change. After the catheter had entered the right atrium, the patient developed a supraventricular tachycardia of 210 beats per minute with symptoms of breathlessness and oppression in the chest similar to his symptoms during exertion and after eating. The arrhythmia spontaneously subsided in 10 minutes.

Case V. D. L. V., a 19-year-old married white woman, a first cousin of J. P., Ronald P., and Robert

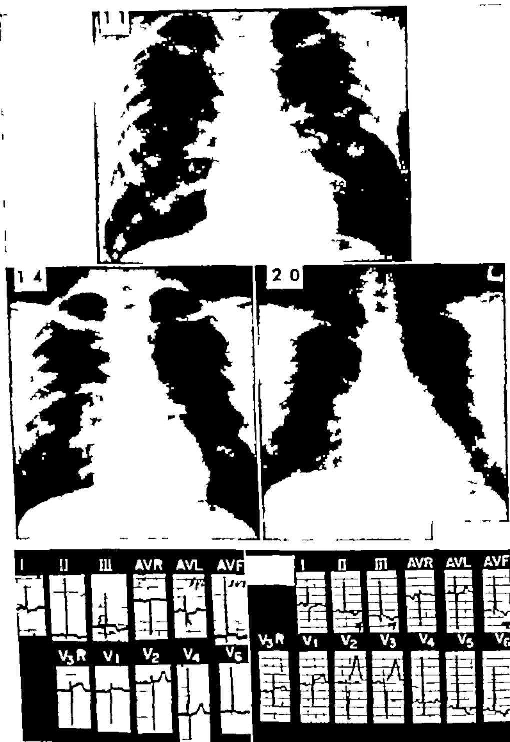


Fig. 4. Case IV, R.P. (4206135). Serial x-ray films and electrocardiograms. ECG at lower left was recorded on Sept. 8, 1958, age 14. ECG at lower right was recorded on Jan. 20, 1964, age 20. Leads II, III, and aVF of the ECG at age 20 are half standardized.

Table I. Cardiac catheterization data

Patient	*Age (yr)*	*Date*	*Pressure*		
			RA	*RV*	*PA*
R.P.	14	Sept. 9, 1958	15/6	33/7	33/11
R.P.	20	June 16, 1964	10/5	42/5-9 body 33/2-10 outflow	32/14
D.L.V.	15	Nov. 10, 1959			
Rest			9/4	35 (−7)−13	30/17
Exercise					56/37
E.F.P.	45	February 1961	8	51/8	60/32
A.L.L.	17	July 1957		66/3	

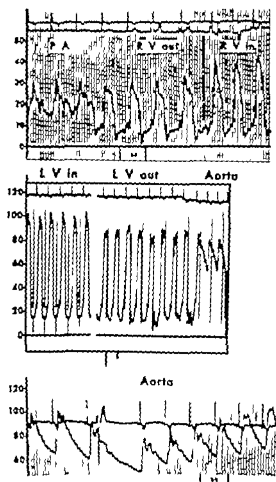


Fig. 5. Case IV. R.P. Pressure tracings (see text).

P. was first seen on Nov. 10, 1959. She was asymptomatic with only a questionable history of decreased exercise tolerance. A heart murmur had been found on a routine examination precipitated by the death of her sister A. L. L. (see Case IX).

Physical examination showed a healthy-looking 15-year-old girl. The jugular venous pulse was normal. Peripheral arterial pulses were normal, but frequent premature beats were felt. The heart was slightly enlarged but precordial activity was normal. A Grade 2/6, late systolic murmur was heard maximally at the fourth left intercostal space between the left sternal border and apex and was widely transmitted over the precordium but not to the neck vessels.

The electrocardiogram (Fig. 6) showed frequent ventricular premature beats and left ventricular hypertrophy. The x-ray film (Fig. 6) showed slight cardiomegaly and slight right atrial prominence.

Cardiac catheterization (Table I) showed an elevated wedge pressure at rest. Right heart pressures and A-V oxygen difference were normal. Supine bicycle exercise doubled the oxygen uptake but resulted in an abnormal widening of the A-V oxygen difference to 7.47 volumes per cent, indicating an inadequate response of cardiac output to exercise. The wedge pressure also rose.

In 1961, at the age of 16, she was still asymptomatic and physical examination and the electrocardiogram were unchanged. On fluoroscopy definite left atrial enlargement was now noted. She became pregnant shortly after this and had an uneventful pregnancy and delivery. She has not been seen since 1961.

We have gathered the following information about other members of the family.

Case VI. E.F.P., a 45-year-old married white woman was the mother of J.P., Ronald P., and

(mm Hg)		Peripheral artery or aorta	A V oxygen difference (vol %)	Cardiac output (L./min)	Cardiac index (L./min./M.²)	Oxygen uptake (c c /min)
Wedge	LV					
14			(Pulmonary arterial saturation 69%)			
20/13	104/15-23 body 87/14-28, outflow	82/56	4 12	6 9	3 4	285
22/15		142/70	4 09	6 2	3 8	255
38/20		170/70	7 47	7 5	4 6	563
24		97/70	(Pulmonary arterial saturation 41%) (Brachial arterial saturation 87%)			
		120/66	6 80			

Estimated
RA Right atrium, *RV* Right ventricle *PA* Pulmonary artery *LV* Left ventricle.

Robert P and the au t of D.L.V. She dated the onset of her illness to age 13 when she had had an acute brief episode of marked nervousness, crying spells dizziness, palpitations and shortness of breath. This occurred shortly after the death of her mother from heart disease. Apparently she suffered further nervous spells but was not disabled, and between the ages of 20 and 38 she delivered six children without complication. At age 38, she first developed significa t dyspnea on exertion, fatigue nd episodes of her heart jumping. At age 42 she was hospitalized in Denver because of fatigue, dyspnea and orthopnea. She was normotensive and had râles in both lungs and an enlarged liver. Examination of the heart revealed only Grade 2 apical mid-systolic murmur. Her hospital course was punctuated by episodes of supra entricular nd entric lar tachycardia. After responding to drug therapy she was discharged.

During the next 3 years her symptoms progressed, nd in J nuary 1961 t age 45 she was hospitalized again. She had an irregular rhythm due to atrial fibrillation, râles in the chest, hepatomegaly and cardiomegaly with a blowing apical systolic mur mur and an early apical diastolic murmur.

The electrocardiogram (Fig 7) showed n intra entricular conduction disturbance. When she had a sinus rhythm, left atrial enlargement was present. The x-ray films (Fig 7) showed cardiomegaly left trial nd left entricular enlargement, and a right aortic arch. Cardiac catheterization (Table I) showed an elevated wedge pressure pulmonary hypertension and a marked reduction in cardiac output as indicated by the low oxygen saturation in the right heart.

I February 1961 a mitral commissurotomy was attempted. No significant stenosis and only minimal mitral regurgitation were noted Microscopic ex amination of the atrial appendage showed no 'lach-

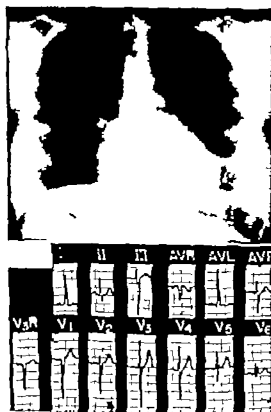


Fig 6 Case V D.L.V (125720), 16-y old female. ECG recorded J n 23 1961 Lead V is half standardized.

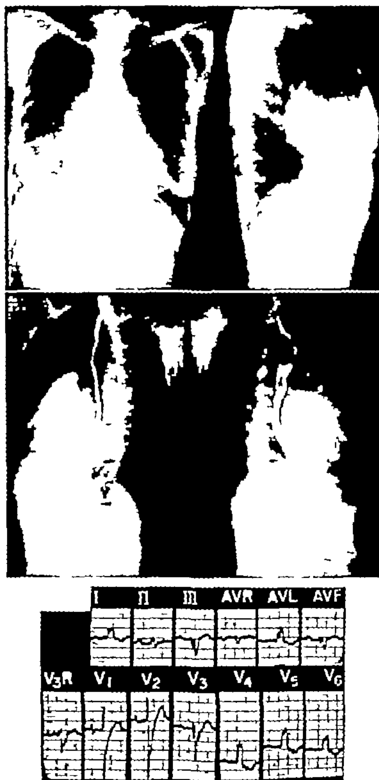


Fig. 7. Case VI. E.F.P., 45-year-old female. ECG recorded Feb. 5, 1961.

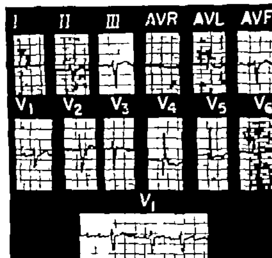


Fig. 8. Case VIII. R.E.V., 39-year-old male. ECG recorded Feb. 5, 1964.

off bodies. The patient had no symptomatic improvement and died 5 months later. No autopsy was performed.

Case VII. Robert P., son of E.F.P. and brother of J.P. and Ronald P., was told of a heart murmur in his early teens and advised to forego sports. However, he did not, and at the age of 15 he suddenly dropped dead while playing football. No autopsy was performed.

Case VIII. R.E.V., a 39-year-old white man, a brother of E.F.P., had no history of rheumatic fever but a heart murmur had first been noted while he was in the Armed Forces during World War II and this had led to his discharge. At age 37 he first developed atrial fibrillation, heart failure, and a saddle embolus. After admission to a Veterans Administration Hospital, his left leg became gangrenous and was amputated above the knee. His arrhythmia did not revert with quinidine and he was discharged on digitalis and anticoagulants. The diagnosis was rheumatic heart disease.

One and one-half years later in February, 1964, the patient was readmitted to the V.A. Hospital because of an episode of pain in the left arm and anterior chest and shortness of breath of a few hours duration. The electrocardiogram (Fig. 8) showed the pattern of an old anterolateral myocardial infarct with peri-infarction block and resultant left axis deviation. This was the same as previous electrocardiograms. The rhythm was atrial flutter with variable A-V block. No evidence of acute infarction appeared on observation, and he was discharged after 3 weeks.

One month later he was readmitted to another V.A. Hospital because of pain in his left leg stump, weakness and swelling of his right leg, and paroxysmal nocturnal dyspnea. Physical examination showed a blood pressure of 100/60 mm. Hg, the pulse rate was 40 per minute and irregular. He had jugular venous distention, 4+ pretibial edema of the right leg, and hepatomegaly. The precordium was quiet, and a short apical systolic murmur was noted. P₂ was widely split. The electrocardiogram showed atrial fibrillation but was otherwise unchanged. He was treated for digitalis intoxication, with a slight increase in heart rate. Although he was scheduled to return for cardiac catheterization, he died suddenly shortly after his discharge. No autopsy was performed.

Case IX. A.L.L., a 19-year-old single white girl, was the sister of D.L.V. Although a heart murmur had been noted at 6 months of age, she had no difficulty until age 17, when she suddenly developed fainting attacks. During one of these episodes, she was found to have complete heart block. She was hospitalized elsewhere in Denver for cardiac catheterization.

Physical examination showed a blood pressure of 110/74 mm. Hg. Pulse rate 40 per minute and regular. The heart was slightly enlarged. S_2 at the pulmonary area was widely split and a Grade 2/6, short ejection systolic murmur was present. She

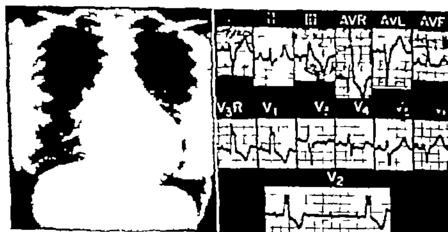


Fig. 9. Case IX. A.L.L., 19-year-old female. ECG recorded July 19, 1957.

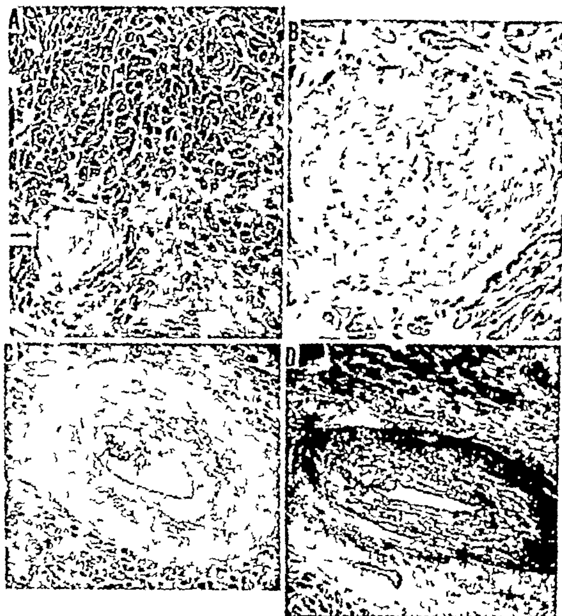


Fig. *10* Case IX, V.L.J. Sections from left ventricle. *A*, Myocardial hypertrophy with interstitial fibrosis. Note scarring near blood vessel (arrow). Hematoxylin and eosin. ×50. *B*, Enlargement of blood vessel seen in *A*, showing medial hypertrophy and narrowing of lumen. Hematoxylin and eosin. ×165. *C*, A larger artery with a thick wall showing degenerative changes. Note the myocardial fibrosis. Hematoxylin and eosin. ×50. *D*, Same artery as that seen in *C*. Most of the thickening is intimal. Verhoeff Van Gieson. ×50.

had a Grade 2/6 blowing systolic murmur at the tricuspid area which increased with inspiration. Atrial sounds were noted.

The x-ray film (Fig. 9) showed cardiomegaly with a right ventricular contour and some left ventricular prominence. The electrocardiogram (Fig. 9) showed 3:1 A-V block and an intraventricular conduction defect of the RBBB type. Cardiac catheterization (Table I) showed right ventricular hypertension and a low cardiac output.

During the next 2 years she was admitted three times to the hospital, each time with more cardiac enlargement, persistent heart block, and eventually refractory congestive heart failure. She died suddenly during her last hospital admission.

Autopsy findings in other organs were primarily those of marked congestive failure. The heart weighed nearly 500 grams, with marked globular enlargement of the left ventricle and with less marked enlargement of the left atrium and right ventricle. The heart valves were normal. There was some subendocardial sclerosis, more marked in the left

ventricle. Microscopic examination (Fig 10) showed myocardial hypertrophy and considerable fibrosis. The fibrosis varied from an increase in interstitial connective tissue in some areas to loss of myocardial fibers and scarring in others. The smaller coronary arteries in the myocardium showed intimal thickening, medial hypertrophy and narrowing of the vessel lumen. These changes were most marked in sections of left ventricle but were also seen in the right ventricle.

Case X R.L.W mother of D.L.W and A.L.L., and sister of E.F.P and R.E.W., has known of a heart condition for years. For the past 5 years she has had acute attacks of sudden weakness, inability to talk, and marked dyspnea. After a few minutes, she develops a sensation of pressure in the chest with radiation into both arms. The attacks suddenly stop after 5 to 60 minutes. She was hospitalized in Lincoln Nebraska, in July 1963 because of the increasing frequency of these attacks during the preceding 6 months.

On examination the blood pressure was 114/78 mm Hg Examination of the heart revealed only a soft apical systolic murmur which was thought to be an innocent murmur A chest x-ray film showed only slight cardiomegaly The electrocardiogram showed one episode of paroxysmal atrial tachycardia. Marked myocardial ischemic changes were also noted She was discharged on digitalis and quinidine with some decrease in the frequency of the attacks.

Case XI C.L., age 15 the youngest daughter of R.L.W., began to have episodes of anterior chest pain which occurred usually on exertion but occasionally at rest. She was treated with nitroglycerin which seemed to help relieve the pain. She had recently developed mild swelling in the feet.

On examination in January 1964 the blood pressure was 110/70 mm Hg Her weight was 135 pounds. A soft apical systolic murmur was heard but otherwise the examination of the heart, lungs, and abdomen was unremarkable The chest x-ray film was negative. The electrocardiogram showed postero-lateral myocardial ischemia." She continued taking nitroglycerin and she was advised to reduce her activity

On the family pedigree (Fig 11) we have shown other members of this family with known heart disease. Dr D G McNamara Houston Texas, has informed us that P H was catheterized and then died. Autopsy showed cardiac hypertrophy A sister has been catheterized and has subaortic obstruction. Two other siblings are unaffected The mother H H died at age 34 of heart disease. A brother of H H M H underwent surgery for subaortic obstruction by Dr Denton Cooley and died

We do not have detailed information about the other members of the family except that they either have heart trouble or have died from it and they are listed as suspected cases.

Discussion

A Inheritance Several patterns of inheritance have been reported. Evans original cases[1] suggested a dominant inheritance, and this has been supported by other reports.[3,4,7,21,31,34,37] Large families studied by Pare and associates,[20] Barry and Hall[34] and Whitfield[19] clearly show an

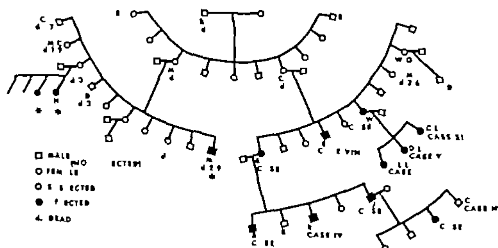


Fig *11* Pedigree of the family reported on. Asterisks indicate that subjects are known to be involved (courtesy of Dr D G. McNamara, see text) Those subjects probably affected are either known to have heart disease or have died from it. Age at death is given if known.

autosomal dominant type of inheritance The family we have studied has the same pattern (Fig 11)

However families suggesting a recessive inheritance have been reported[illegible] One family in which two siblings and an uncle were involved but in which the parents of the siblings were normal suggests the possibility of a dominant inheritance with incomplete expression and apparent skipping of a generation

Some of the differences in the mode of inheritance may be due to variation in penetrance of the defect. It may not express itself in every generation If it does, it may do so mildly and only late in life Another likely possibility is that families with familial cardiomyopathy may have different genetic defects (i e there may be genocopies) some of which may be inherited in a recessive manner The possibility of a common environmental agent causing heart disease in a number of members of a family cannot be ruled out but is most unlikely in successive generations Toxoplasmosis was reported as such an example[7] but this seems to be unlikely[16]

Some authors have questioned the relationship of inherited neuromuscular disorders associated with cardiomyopathy to familial cardiomyopathy There are two reports of familial heart disease with inherited neuromuscular disease, Friedreich's ataxia in one and pseudohypertrophic muscular dystrophy in the other in which some members of these families had heart disease and others had ataxia or muscle weakness. Only one subject had both heart disease and muscular dystrophy These families could easily represent a coincidence of uncommon diseases. None of the large families studied including our own show a similar association.

B Clinical picture The original syndrome described by Evans of young adults with a striking predisposition to arrhythmias and proneness to sudden death has been noted in most of the families reported on. In the family of our report, sudden death in the second third or fourth decade of life has been quite common Stokes-Adams syncope also noted originally by Evans, occurred in one member of this family (Case VIII) Paroxysmal tachycardias, mainly supraventricular and atrial fibrillation were even more common occurring at some time in Cases VI VIII and probably IX

Early symptoms of compromised cardiac reserve such as decreased exercise tolerance and dyspnea on exertion, have also been common findings. Refractory congestive heart failure not due to an uncontrolled arrhythmia has occurred in this entity but seems to be less frequently encountered than arrhythmias When heart failure occurs, it seems to affect the older subjects (Cases VI and VII) These same comments apply to thromboembolic complications from mural thrombi. It seems likely that arrhythmias may cause the death of many younger subjects before the end-stage manifestations of heart failure and mural thrombi develop.

Chest pain mimicking angina pectoris may also occur There is insufficient information to determine how often this occurs in the absence of subaortic obstruction, but Braunwald and Aygen suggest that it is common.[illegible]

The findings on physical examination of the heart vary with the specific location and severity of the myocardial involvement. Prominent third and fourth heart sounds, an irregular rhythm and insignificant or no murmurs are the usual findings (Cases I II III and V) The murmurs of mitral or tricuspid insufficiency may be heard particularly if congestive heart failure is present (Case IX) These are typical features of any cardiomyopathy However some patients may have pathologic murmurs indicating obstruction to outflow from either ventricle, usually the left ventricle (Case IV) Cardiac hypertrophy particularly of the ventricular septum which encroaches on the outflow area of either ventricle is now a well recognized cause of outflow obstruction.

Some patients have been reported to have apical diastolic murmurs of mitral stenosis (Case VI Case VII?) In some cases, this may be due to a mistaken interpretation of a third heart sound However muscular hypertrophy may distort and narrow the mitral valve leading to obstruction of inflow into the left ventricle, thus mimicking mitral valve stenosis.[illegible]

C Electrocardiogram The electrocardio-

gram has most commonly shown QRS abnormalities of left ventricular hypertrophy and intraventricular conduction defects of different kinds and abnormal P waves.[26,27] The QRS abnormality may suggest an old myocardial infarct[27] as in Case VII and under these circumstances only an autopsy can rule out coronary artery disease. A-V conduction defects supraventricular tachycardias, ventricular tachycardia, and atrial fibrillation have all been commonly noted. Pre-excitation has also been found in some patients.

Recently Karn and associates[27] showed that the electrocardiographic findings in familial cardiomyopathy progressed from those of ventricular hypertrophy particularly septal hypertrophy initially to those of intraventricular conduction disturbances with lower voltages, later. Pare and associates[28] also noted that the more bizarre electrocardiograms were found in the more severely affected subjects. The findings in our patients agree with these observations. From our observations in Cases II, III and V, we also agree that the electrocardiogram is probably the most sensitive objective indicator of heart disease in this entity.

D. X-ray films. The chest x-ray film is nonspecific. The common features are cardiomegaly with left ventricular and slight left atrial enlargement. However, as in Case VI, the heart may show a mitral configuration with significant left atrial enlargement and right ventricular enlargement. This might be due to muscular hypertrophy producing obstruction of inflow into the left ventricle. Pare[28] has also reported that localized septal hypertrophy may produce an anterior bulge mimicking right ventricular enlargement. The presence of an enlarged heart with left ventricular prominence in the face of an inconspicuous aorta should suggest the possibility of primary myocardial disease.

E. Cardiac catheterization (Table I). Relatively few patients with this entity have undergone cardiac catheterization,[21 1 .20,33 21] and in the past few years they have mainly been patients with muscular subaortic obstruction.

Those patients without obstruction may show normal right heart and wedge pressures and normal cardiac output at early stages of the disease[21] or the only abnormalities may be an elevated wedge pressure and an abnormally low cardiac output on exercise (Cases IX and X). The elevated wedge and at times right atrial pressures reflect elevations in end-diastolic ventricular pressures and indicate early changes in compliance of the ventricles.[21] As the disease progresses, significantly elevated wedge and right heart pressures and an abnormally low cardiac output at rest are found (Cases XI and IX).

The physiologic findings in muscular subaortic obstruction are well known.[31,32] Case IX shows the typical arterial tracing with a rapid upstroke and prominent percussion wave and the lower pulse pressure of the normal beat following the premature beat (Fig. 5). The systolic pressure of the normal beats takes a number of beats to gradually reach the systolic pressure present before the premature beat. We have noted this finding in every patient with muscular subaortic obstruction whom we have studied.[34] This suggests that it takes a number of heartbeats after a premature beat for the muscular obstruction, the stroke volume, and the residual ventricular volume to return to levels present before the premature beat.

Braunwald and Aygen[31] have supplied physiologic data on a number of patients who had signs of cardiomyopathy without obstruction. Some of them developed left ventricular gradients after receiving isoproterenol. It seems clear that the primary myocardial disease may produce a spectrum from hypertrophy with no obstruction to hypertrophy with severe obstruction and all gradations in between.

Because of the propensity to arrhythmias in these patients, cardiac catheterization has been considered to be dangerous. Nevertheless, most of the patients reported as undergoing catheterization have had no difficulties during the procedure. Braunwald and associates[32] report one case in which ventricular fibrillation occurred after right and left heart catheterization but was converted successfully. Our Case IV developed a supraventricular tachycardia after isoproterenol was given. Prior to this, no irritability of the heart had been noticed. Although the risk may be somewhat higher than usual in these

patients, particularly for left heart catheterization the procedure is probably indicated if obstruction is suspected clinically.

F. Pathology. On gross examination the heart may show generalized ventricular hypertrophy and varying degrees of dilatation or it may show an asymmetrical hypertrophy usually involving the interventricular septum and encroaching on the outflow tract of the left ventricle and sometimes on that of the right ventricle. Encroachment on the inflow tract with distortion and narrowing of the mitral valve has been reported.[11] Pare and associates[24] have shown that asymmetrical and generalized hypertrophy may occur in the same family. They also noted hypoplasia of the aorta and medium-sized arteries and they thought that hypoplasia might be part of the inherited disorder. However hypoplasia may well be due to low systemic blood flow.[16,27]

The microscopic picture has been more varied. Myocardial hypertrophy has been a constant finding but the amount of myocardial fibrosis has varied considerably from none to gross scarring. Garrett and co-workers[12] suggested that those cases without fibrosis were rarer than and different from those with fibrosis. However this difference is probably merely one of degree. Evans and Gaunt and Lecutier[4] found microscopic evidence of vacuolation and glycogen accumulation in the heart, whereas Battersby and Glenner[22] and Barry and Hall[2] found a nonmetachromatic polysaccharide material deposited in myocardial fibers. Most authors have found no abnormal depositions on microscopic examination. Although inflammatory cells are usually not pre- a few cases there has been enougl n of cells to indicate a myocardi the cases of asymmetrical hyperi haphazard arrangement fi- bers has been seen suggesti

Only a few reports men lesions. Pare[24] reported change the aorta and m arteri ed no intra vascul A few authors involven aller terres wi intimal thic and encro lumen

The sections of the myocardium of Case VIII which we have reviewed show considerable fibrosis of the myocardium and thickening of the intima and media of the smaller coronary arteries in the myocardium with narrowing of the lumen. No inflammatory element is present. These lesions appear to be the same as those illustrated in Battersby and Glenner's article.[22] Because of its extensiveness one must consider the possibility that the vascular lesion may be primary with myocardial involvement a secondary result.

The differences in pathologic findings within the same family indicate that considerable variation exists in the same disease. It also is quite likely that some of the differences between families with familial cardiomyopathy may be due to different basic defects which we are unable to distinguish now.

Summary

A large family with familial cardiomyopathy inherited as an autosomal dominant trait is reported on. One subject developed muscular subaortic and infundibular obstruction. The genetic clinical electrocardiographic radiologic and pathologic features found are compared with those previously reported. The variation in clinical and pathologic findings is emphasized. One autopsied case showed thickening of the walls of the small coronary arteries which raises the possibility that some of these ca may be due to disease of the small cor arteries.

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Relationship of gross myocardial infarction to severity of coronary atherosclerosis in the young male

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Myocardial infarction is generally thought to occur mainly on the basis of coronary atherosclerosis, and particularly when the atherosclerosis is of severe degree. Yater and associates[1] reported on coronary disease in the young soldier of World War II. Contrary to the above-mentioned assumptions, the authors noted that in 114 cases having gross myocardial infarction at necropsy, 48.2 per cent had thrombotic occlusion alone, whereas only 23.7 per cent had sclerotic occlusion alone. These findings suggest that abnormality of the clotting mechanism was more instrumental in coronary occlusion than was atherosclerosis. This result is particularly interesting in view of Morris' observation[2] that atheroma of the walls of coronary arteries has not increased during this century, but that severe obstruction of the coronary lumen has. According to Morris, the epidemiologic evidence suggests that much more than mural atheroma is involved in coronary occlusion. Similarly, Parrish,[3] in a necropsy study, found that those patients with ischemic heart disease who died in the period 1935-1944 had more severe coronary atherosclerosis than those who died in the period 1945-1955; there was also a suggestion that coronary artery clots were less prevalent in the period 1935-1944.

These observations question the above-mentioned premise that myocardial infarction usually results from coronary atherosclerosis and that the sclerosis is severe. This is an important question. Studies of clinical myocardial infarction, even in the young, presume that the illness is based on coronary sclerosis of a severe degree. Is the presumption based on fact? Or, is the clotting mechanism the major factor, and the atherosclerosis incidental or merely a predisposing condition for the development of a thrombus?

We are planning a study in the young male with clinically manifest myocardial infarction, seeking differences in lipid metabolism which may be associated with the pathogenesis of atherosclerosis. The foregoing questions raised doubt of the validity of the almost axiomatic assumption that infarction is related to severe sclerosis. A review of the literature revealed no report other than that of Yater's group giving exact data on the relationship of gross myocardial infarction to the degree of severity

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of coronary atherosclerosis. In a report by Wartman and Hellerstein[1] on the frequency of heart disease in 2 000 consecutive autopsies, 26 of 41 patients with myocardial infarction but without coronary thrombosis had marked or occlusive coronary atherosclerosis among those with infarction *and* coronary thrombosis an unspecified number (most) had moderate to severe coronary arteriosclerosis.

Because of the doubts raised the authors investigated the question in a relatively recently autopsied population of young males.

Method

Autopsy protocols of the Institute of Pathology Western Reserve University from 1959 through mid July 1962 inclusive were used They totaled 1 974 Of these approximately 10 were not available for review From the remainder were selected all records of men who were 30 to 49 years old inclusive a total of 105 For these 105 the general nutritional state recorded in the protocol was noted The terms used to describe the state of nutrition were few in number and readily fell into two groups (1) terms describing the poorly nourished (poor cachectic emaciated undernourished ") (2) terms describing those not poorly nourished (adequate fair good normal obese, well nourished) The poorly nourished cases were removed from the study * These totaled 26

The protocols of the remaining 79 cases were then examined in detail Record was made of the presence or absence of gross myocardial infarction whether recent or old Record was also made of the degree of atherosclerosis of the right left, left anterior descending and left circumflex coronary arteries. The terms used to describe coronary atherosclerosis were relatively few in number and fell logically into four groups of increasing degree of severity (1) "normal none" (2) mild" slight" minimal, (3) "moderate moderately severe" (4) "severe marked occlusive. For tabulation these groups were assigned the values 0 1 2 and 3 respectively The degree of atherosclerosis recorded was a consensus derived from review of the entire protocol gross description microscopic description and final pathologic diagnosis. In four instances this consensus differed from the final pathologic diagnosis considered alone and all in the same direction four cases considered to be of moderate degree (2) in the final diagnosis were considered to be severe (3) when the entire protocol was reviewed The most marked degree of atherosclerosis found in the coronary arteries designated above was used The protocols in some instances did not detail in which particular coronary artery the described degree of atherosclerosis was found so that in the final analysis the degree of atherosclerosis used in all cases was the most severe found anywhere in any one of the arteries.

Results

Of the 79 cases reviewed in detail 4 could not be used In 3 of these the degree of atherosclerosis was not noted in the protocol and in the fourth a case of Marfan s syndrome with aortic insufficiency the nature of the gross scarring of the myocardium was in doubt. It consisted of local (1 mm) scattered fibrous scars which according to the epicrisis, were consistent with ischemia from the clinically present chronic congestive heart failure It was thought better to omit this case. Seventy five cases remained and these form the basis of the analysis.

Table I shows the relationship of the degree of coronary atherosclerosis to the presence or absence of gross myocardial scar Of the 12 patients who died of myocardial infarction 11 (92 per cent) had severe (grade 3) atherosclerosis Of the 3 patients who died of other cause but had gross myocardial scar all 3 had severe atherosclerosis. It is seen then that of 15 patients having gross myocardial infarction at autopsy 14 or 93 per cent had severe coronary atherosclerosis. Sixty patients died of cause other than myocardial infarction and did not have gross myocardial scar Of these only 5 (8 per cent) had severe sclerosis. The difference in frequency of severe coronary atherosclerosis in those with gross myocardial infarction (93 per cent) and in those without it (8 per cent) is significant ($P < 2$ 10)

The average age of those dying of myocardial infarction or having gross scars at autopsy was 45 1 years The average age of

Table I Distribution of degree of coronary atherosclerosis according to the presence or absence of gross myocardial infarction

Cause of death	*Degree of atherosclerosis* 0	1	2	3	*Per cent with severe atherosclerosis*
	Number of patients				
Acute myocardial infarction			1	11	92
Other than acute myocardial infarction					
Gross myocardial scar present				3	100
No gross myocardial scar present	15	24	16	5	8

those [illegible]ng gross scars was 41 0 years. In view [illegible]he known relationship between coronary [illegible]erosclerosis and age the difference [illegible]ity of atherosclerosis between the [illegible] groups described above could pos[illegible] have been explained by the difference [illegible] age For this reason the data were [illegible]alyzed in the following manner The age at death of the youngest person having [illegible] myocardial infarction was 39 years. All persons less than 39 years of age without myocardial scars a total of 18 were omitted Of the remaining 42 patients, only 4 (10 per cent had severe sclerosis. The difference in frequency of severe coronary atherosclerosis in those with gross myocardial infarction (93 per cent) and in those without it (10 per cent) remained statistically significant (P = 1 4 10)

Discussion

Since the elucidation of myocardial infarction as a clinical entity the association of such infarction with severe coronary atherosclerosis has been accepted as a truism. Accordingly the authors intended to use the clinical development of myocardial infarction as evidence of severe coronary atherosclerosis in a projected study of certain aspects of lipid metabolism A search was first made however for documentation of the assumed relationship of gross myocardial scars to severe coronary atherosclerosis. None could be found and furthermore Edwards[4] indicated that to his knowledge there are no reports on the subject. Rather the study of Yater and his associates[5] incidentally showed that in young males with gross myocardial scars 48 2 per cent had only thrombotic occlusion whereas 23 7 per cent had only sclerotic occlusion This is particularly interesting in light of recent emphasis on hypercoagulability of the blood in certain clinical conditions.[7] Further analysis of Yater's figures shows that in those without myocardial scars, 34.8 per cent had thrombotic occlusion alone whereas 44 0 per cent had sclerotic occlusion alone This apparent negative association between the presence of sclerotic occlusion alone and the presence of myocardial infarction added to lack of documentation of the generally accepted association of myocardial infarction and severe coronary atherosclerosis prompted this study It is evident from our results that what has seemed obvious is indeed true at least in this autopsy population

The extension of findings in an autopsy population to a living one may lead to error [8] Although one would prefer not to extrapolate from an autopsy to a living group there seems to be no alternative in this case. Few conclusions can be drawn however from the figures in Table I concerning the proportion of the living population without gross myocardial scars which has undiagnosed severe coronary atherosclerosis. All that can be said is that severe coronary atherosclerosis is found to a limited extent in people dying from causes other than myocardial infarction. There is also much undefinable selection in hospital admission and in those cases coming to

necropsy A study seeking to avoid the limitations imposed by an autopsy population particularly one derived from a hospital population might accomplish this in effect by the use of postmortem examinations done in a group dying unexpectedly in a general catastrophe This type of information is difficult to obtain although an approach has been made in a selected population.[9, 10] Our autopsy findings however do concur completely with the generally accepted clinicopathologic impression There fore, despite the above-mentioned possible criticisms the findings are interpreted as evidence of an association between the presence of myocardial infarction and severe coronary atherosclerosis.

Autopsy studies are subject to other criticisms and limitations. There is perhaps the natural bias of the pathologist to seek out more assiduously coronary atherosclerosis in those cases coming to necropsy with a clinical diagnosis of myocardial infarction than in those without such a diagnosis. This seems not to have been the case here although the numbers are small the patients who died of other than myocardial infarction but who had gross myocardial scars were found to have severe atherosclerosis.

Our method of determining the severity of atherosclerosis may be criticized It called for the recording of the most marked degree of atherosclerosis found in any one of the main arteries. Thus, coronary arteries generally free of atherosclerosis but having only one occlusive plaque were graded 3 whereas coronary arteries with moderate atherosclerosis spread throughout were graded only 2 In view of reports[11, 12] which showed that the extent of atherosclerosis *is not necessarily a factor in sudden* death our method seems to be reasonable.

The clinical implications of the study are apparent. Myocardial infarction is found to be related to severe but not necessarily widespread coronary atherosclerosis. In any study of such arteriosclerosis therefore whether from the point of view of causation or amelioration or cure " the clinical occurrence of acute myocardial infarction properly diagnosed[13] does indicate the presence of severe atherosclerosis at some point in at least one of the main coronary arteries. In clinical practice the finding of two or more of certain electrocardiographic abnormalities would indicate the presence of gross myocardial scars or severe coronary atherosclerosis.[14]

Summary

A necropsy study was made of the relationship of the degree of coronary atherosclerosis to the presence of gross myocardial infarction in men who were 30 to 49 years of age inclusive. Those with wasting disease were excluded The controls were those of the same sex and age group who did *not* have a gross myocardial lesion at necropsy The results showed that in this group of young males the presence of gross myocardial infarction is significantly related to the presence of severe coronary atherosclerosis

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Experimental and laboratory reports

The effects of "dry" heat on the circulation of man. Cerebral hemodynamics

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Data presented by us in previous reports have documented the effects of a 2-hour exposure to a relatively dry warm environment (98°F, 40 per cent relative humidity) on the general, splanchnic,[1] renal,[2] and coronary[3] hemodynamics in normal resting man, as well as in patients who had heart disease that involved primarily the left ventricle. The significant findings in all groups of subjects were decreases in the systemic, pulmonary, splanchnic, and renal resistances, due to significant decreases in the peripheral arterial pressure with no change in the observed blood flows, except for a significant decrease in the coronary flow. However, coronary vascular resistance remained unchanged, and the calculated left ventricular work[4] as well as left ventricular myocardial oxygen consumption[4] decreased significantly.

The object of this report is to present and comment on data similarly collected which relate to the cerebral blood flow as determined by unilateral jugular bulb catheterization in intact, resting man, employing the nitrous-oxide method of Kety and Schmidt.[5]

Materials and methods

Group A. Double controls. These patients were free of heart disease except for B. J. and J. G. (Table I), who had left ventricular hypertrophy without heart failure. Two sets of determinations were obtained at an interval of 2 hours in the comfortable environment only (73°F and 40 per cent relative humidity). These data served as the control and comparative determinations for the method.

Group B. Subjects free of heart disease.

Group C. Subjects with enlarged left ventricles who were not in left ventricular failure at rest (pulmonary wedge pressures less than 10 mm. Hg).

Group D. Subjects with enlarged left ventricles who were presumably in left ventricular failure (resting wedge pressures greater than 12 mm. Hg). Two of these were also in right-sided heart failure (D.Mc. and W. T., Table IV), as evidenced by elevated right ventricular end-diastolic and right atrial mean pressure.

The patients were all afebrile. The hematocrit levels ranged from 40 to 48 per cent, obviating the technical error inherent in solubility differences of the

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nitrous oxide[3] in anemic subjects. The ages ranged from 22 to 75 years; however, the neurological examination was normal; none had had known cerebrovascular accidents and clinically there was no reason to suspect the presence of significant obstruction of the extracranial cerebral arteries. In this fashion an attempt was made to reduce the error inherent in differential side-to-side intracranial mixing when flow is determined by unilateral sampling.[4] Complete anatomic normalcy of the cerebral circulation could not be unequivocally accepted, however, since arteriography was not performed in any of the subjects.

The studies were performed with the patients in the postabsorptive state. Phenobarbital (0 1) was given the night before and pentobarbital Na (0 1) on the morning of the study. The patients remained drowsy throughout the procedure and many intermittently slept lightly. After determination of the central venous pressures, via an antecubital vein cutdown with a No. 7 bird's-eye catheter, the latter was withdrawn from the heart and introduced into either the right or left jugular bulb. Positioning was checked fluoroscopically at the beginning and at the end of the procedure. An arterial needle was placed into the ipsilateral brachial artery. After a 20-minute period of stabilization the con

Table I. Group A. Individual data for 10 subjects in whom all determinations were made at 73°F and 40 per cent humidity

Patient	Race Sex B.S.	Diagnosis		Heart rate	PBA	CBF	AVD	CMRO	CVR
B I	N F	Diastolic hypertension	C	71	168/100 (129)	52	5 41	2 8	2 48
	1 64		2 hr	73	175/101 (133)	62	5 50	3 4	2 14
J G	W M	HCVD ASHD	C	106	172/117 (137)	47	8 18	3 8	2 91
52	1 84		2 hr	108	173/120 (138)	44	7 46	3 3	3 14
E V N	W M	Regional enteritis	C	74	132/ 80 (100)	48	6 54	3 1	2 08
59	1 69		2 hr	72	138/ 84 (103)	47	9 35	4 4	2 19
V B.	W M	Chronic alcoholism	C	52	103/ 56 (72)	43	5 14	2 2	1 67
49	1 77		2 hr	54	87/ 49 (63)	36	5 60	2 0	1 75
E.T	N M	Pneumonia, recovered	C	84	144/ 90 (112)	41	7 34	3 0	2 73
56	1 89		2 hr	84	149/ 93 (117)	45	6 75	3 0	2 60
J B	N M	Peripheral neuropathy	C	84	129/ 76 (99)	40	6 68	2 7	2 47
59	1 81		2 hr	84	147/ 90 (114)	44	6 47	2 8	2 59
A.H.	N M	Gastric ulcer	C	65	162/ 98 (128)	48	7 04	3 4	2 67
59	1 8		2 hr	60	168/ 98 (126)	52	7 01	3 6	2 42
E.R	W M	Post phlebitis syndrome	C	75	122/ 71 (93)	56	6 54	3 7	1 66
60	1 90		2 hr	83	116/ 71 (89)	58	6 37	3 7	1 53
L.S.	W M	No disease (volunteer)	C	80	130/ 78 (96)	45	6 33	2 8	2 13
22	1 86		2 hr	75	135/ 82 (100)	46	6 35	2 9	2 17
T J	W M	No disease (volunteer)	C	78	146/ 85 (108)	41	6 14	2 5	2 63
24	1 80		2 hr	74	140/ 82 (100)	47	5 95	2 8	2 13

*Corrected central venous pressures.
PBA: Brachial arterial pressure (mm. Hg); the mean pressure is given in parentheses. CBF: Cerebral blood flow (ml./100 Gm./min.). AVD: Brachial arterial jugular venous oxygen difference (vol.). CMRO$_2$: Rate of cerebral oxygen uptake (ml./100 Gm./min.). CVR: Cerebral vascular resistance (PBA m/CBF). C and 2 hr: Determinations obtained initially and at the end of 2 hours, respectively.
HCVD: Hypertensive cardiovascular disease. ASHD: Arteriosclerotic heart disease.

trol determinations were made. The patients in Groups B C and D were then placed in a constant temperature room (preheated to 98°F and having a relative humidity of 40 per cent) and were covered only with suitable small towels. After 2 hours all determinations were repeated and the experiment was terminated

Cerebral blood flow (CBF) was measured by the nitrous-oxide technique of Kety and Schmidt[3] and expressed as milliliters per 100 grams of brain per minute. Nitrous-oxide tensions were determined manometrically on the Van Slyke apparatus In all but 3 patients, appropriate arterial samples were obtained after the fifth minute of sampling for pH (Cambridge microelectrode) and carbon dioxide content (Van Slyke and Neill)[7] The nomogram of Singer and Hastings[10] was used to calculate the pCO_2. Arterial and jugular venous samples for oxygen content were obtained just before and at the end of the flow run and the average values of the spectrophotometrically determined levels[1] were employed for the calculation of the brachial arterial–jugular venous oxygen difference (AVD) Pressures were transduced via P23AA Statham strain gauges and inscribed on a direct writing Sanborn oscillograph Mean pressures were integrated electrically Cerebrovascular resistance (CVR) and rate of cerebral oxygen utilization ($CMRO_2$) were calculated by the appropriate formulae and expressed respectively as arbitrary resistance units and as milliliters of oxygen per 100 grams per minute

Table II *Group B Individual determinations for 10 subjects with normal hearts*

Patient, Age (yr)	*Race Sex B S*	*Diagnosis*		*Heart rate*	*PBA*	*CBF*	*AVD*	*CMRO*	*CVR*
T S 52	W,M 1 74	Alcholism, diabetes	C 2 h	88 105	142/85 (112) 135/87 (104)	48 42	6 24 7 14	3 0 3 0	2 33 2 47
L. R. 49	W,M 1 62	Myotonia dystrophica	C 2 hr	80 82	134/86 (105) 121/76 (93)	39 47	6 19 6 78	2 4 3 2	2 69 1 98
T C. 37	W,M 1 83	Chronic alcoholism	C 2 hr	79 96	130/80 (103) 118/75 (93)	42 44	6 23 6 53	2 6 2 9	2 45 2 11
R. G 50	N,M 1 80	Duodenal ulcer inactive	C 2 hr	90 95	132/78 (101) 128/75 (97)	53 57	7 45 7 18	3 9 4 1	1 90 1 70
S. J 66	W M 1 71	Systolic hypertension	C 2 hr	80 84	184/92 (131) 174/88 (123)	31 35	7 18 7 79	2 2 2 7	4 20 3 51
G B. 42	W,M 1 79	Pneumonia, resolved	C 2 hr	76 84	123/73 (95) 120/68 (91)	30 38	7 12 5 26	2 1 2 0	3 16 2 39
T J 58	W,M 1 90	No disease	C 2 hr	65 77	145/88 (113) 118/74 (94)	34 39	9 45 8 74	3 2 3 4	3 32 2 41
W W 36	W,M 1 88	No disease	C 2 hr	72 84	134/84 (108) 120/72 (90)	48 44	6 62 6 58	3 2 2 9	2 25 2 04
L. C. 61	N,F 1 53	Chronic alcoholism	C 2 hr	81 90	150/65 (90) 116/54 (73)	54 48	5 79 6 17	3 1 3 0	1 76 1 52
C. F 36	W,M 1 96	No disease	C 2 hr	77 88	122/75 (94) 104/66 (80)	42 43	7 00 7 87	2 9 3 4	2 24 1 86

Initial determinations (C) obtained at 7[illegible]° F and 40 per cent humidity Experimental determinations (2 hr) obtained after 2 hours of exposure to 98° F and 40 per cent humidity For key to abbreviations, see footnotes to Table I.

*Table III Group C Individual determinations for 10 subjects with enlarged left ventricles and normal wedge pressures**

Patient, Age (yr)	Race Sex B.S.	Diagnosis		Heart rate	PBA	CBF	AVD	$CMRO_2$	CVR
R. H	N M	HCVD	C	57	199/112 (147)	46	9 28	4 3	3 19
58	1 74		2 hr	72	152/92 (116)	52	9 31	4 8	2 23
S. D	W M	ASHD	C	78	130/77 (101)	52	5 44	2 8	1 94
75	1 69		2 hr	87	121/74 (90)	46	5 70	2 6	1 96
D H	W M	HCVD and ASHD	C	72	254/111 (165)	31	6 08	1 9	5 32
69	1 80		2 hr	78	242/107 (157)	46	6 61	3 0	3 41
J S.	N M	ASHD	C	84	123/76 (9)	40	7 82	3 1	2 30
65	1 86		2 hr	90	120/72 (86)	38	7 47	2 8	2 26
A. J	N M	ASHD	C	60	142/89 (112)	39	5 96	2 3	2 87
51	1 74		2 hr	70	122/84 (99)	36	7 18	2 6	2 75
E. H	N F	RHD MI	C	78	140/88 (107)	38	7 15	2 7	2 81
40	1 86		2 hr	88	136/81 (99)	43	6 56	2 8	2 30
F S.	W M	ASHD	C	69	175/62 (105)	40	6 25	2 5	2 62
72	1 64		2 hr	84	153/60 (91)	38	6 98	2 6	2 39
G. S	W M	ASHD	C	94	145/90 (113)	47	5 93	2 8	2 40
56	1 75		2 hr	102	132/76 (98)	50	5 82	2 9	1 96
D F	N F	HCVD	C	58	252/112 (158)	34	6 33	2 2	4 65
62	1 53		2 hr	69	212/84 (119)	40	6 30	2 5	2 98
I H	N F	HCVD	C	84	203/117 (150)	42	7 52	3 1	3 57
40	1 66		2 hr	92	168/97 (130)	50	6 17	3 0	2 60

*Procedure as for patients in Table II
RHD Rheumatic heart disease *MI* Mitral insufficiency For key to other abbreviations, see footnotes to Table I.

Results

The individual data for the 4 groups are presented in Tables I-IV Averages, per centile changes, and significance analyses are shown in Table V

The control group showed no change in any of the determinations which were made.

Among the experimental groups, the heart rate increased and the mean brachial arterial pressure decreased significantly Cerebral blood flow * brachial arterial-jugular venous oxygen difference and cerebral oxygen uptake* remained unchanged Arterial pCO_2 increased slightly but significantly the average data are shown in Table VI

Cerebral vascular resistance decreased significantly

The increases in the heart rate and in arterial pCO_2 and the decreases in the brachial arterial pressure and the cerebral vascular resistance were also significant when compared to the comparable data determined for the control group.

Discussion

Cerebral blood flow remains unaltered and cerebral vascular resistance decreases during the decline in the brachial arterial pressure induced by a short term exposure to a dry and warm environment. These findings are in accord with the previous

*The average CBF and $CMRO_2$ are lower than the usually accepted average norms ([illegible] and 3 3 c.c.) This may be explained by the arbitrary reduction of the determined values by 10 per cent and the use of barbiturate sedation which was enough to render the patients quite drowsy

*Table IV Group D Individual determinations for 10 subjects with enlarged left ventricles and elevated wedge pressures**

Patient Age (yr)	Race Sex B.S.	Diagnosis		Heart rate	PBA	CBF	AVD	CMRO	CVR
P S.	N,M	HCVD	C	60	183/101 (133)	49	5 72	2 8	2 1
47	1 82		2 hr	74	161/87 (113)	52	5 61	2 9	2 17
D Mc †	N,M	ASHD	C	76	138/90 (107)	56	9 00	5 0	1 91
59	1 86		2 hr	83	130/85 (103)	67	8 48	5 7	1 54
D H	W,M	ASHD systolic hypertension	C	78	171/96 (122)	33	5 49	2 9	2 30
63	1 70		2 hr	78	158/84 (110)	58	5 32	3 1	1 90
L. B.	W,M	RHD MI	C	84	128/74 (95)	43	5 89	2 5	2 28
35	1 79		2 hr	90	118/69 (82)	37	6 74	5	2 22
M L.	N,M	ASHD	C	74	130/77 (100)	42	7 63	3 2	2 38
39	1 69		2 hr	86	114/66 (84)	36	8 92	3 2	2 33
W T ‡	N,M	Idiopathic cardiomegaly	C	88	106/78 (90)	45	8 12	3 6	2 00
32	1 83		2 hr	96	94/67 (76)	42	8 00	3 4	1 81
H F	N,F	RHD aortic stenosis and insufficiency	C	68	130/61 (85)	48	6 43	3 1	1 77
35	1 90		2 hr	75	122/56 (78)	42	6 9	2 9	1 86
M C.	N,M	Idiopathic cardiomegaly	C	108	134/104 (116)	38	7 11	2 7	3 05
25	1 71		2 hr	118	125/88 (102)	40	6 62	2 6	2 55
J D	N,F	HCVD	C	89	246/122 (161)	40	6 42	2 6	4 02
52	1 84		2 hr	101	218/100 (140)	51	6 00	3 1	2 4
F M	N,M	RHD aortic and mitral insufficiency	C	63	174/84 (121)	37	7 59	2 8	3 27
27	1 78		2 hr	68	146/72 (104)	34	6 95	2 4	3 06

*Procedure as for patients in Tables II and III.
†Pre 79/13
‡Pre 42/14
For key to abbreviations, see footnotes to Table I.

demonstrations by others that, no matter how induced mild to moderate reductions in arterial pressure are attended by a maintenance of the control cerebral blood flow in association with a dilatation of the cerebral vessels In the case of the present experiments, compensation for the reduced perfusion pressure[1] was attained by a reduction in cerebral vascular resistance presumably due to the vasodilating effect of the increased arterial pCO_2 whether any other mechanism was operative can not be stated

The demonstrated increase in the arterial pCO_2 was similar to a significant rise noted in patients exposed to a warm and dry environment, and reported in a previous study In that it may account for the decrease in CVR this serves a "useful purpose and on the basis of previous data, may be explained by an increased body temperature with an increased total tissue catabolism in the presence of an unchanged minute ventilation.

In conclusion the decrease in arterial blood pressure attendant on a short term exposure to a warm and dry environment is associated with the maintenance of a

Table V. Averages, percentile changes, and significance analyses for the four groups

	Heart rate	PBA	CBF	AVD	$CMRO_2$	CVR
A. Control						
C	77	107	46	6 51	3 0	2 54
2 hr	77 0%	108 + 0 9%	48 + 1 3	6 68 + 2 3	3 2 + 6 7	2 60 + 13 7
1 (C vs 2)	> 5	> 5	> 5	> 5	< 2 > 1	< 1 > 05
B. Normal heart, heat						
C	79	106	42	6 93	2 9	2 63
2 hr	88 + 11 4	94 − 11 3	44 + 4 8 %	7 00 + 1 0%	3 1 + 6 9	2 20 − 16 4
1 (C vs 2)	< 001	< 001	< 3 > 2	> 5	< 1 > 05	< 005 > 001
C. Enlarged left ventricle, normal wedge pressure, heat						
C	73	125	41	6 78	2 8	3 17
2 hr	83 + 13 7	108 − 13 6 %	44 + 7 3	6 81 + 0 4 %	3 0 + 7 1	2 48 − 21 8%
1 (C vs 2)	< 001	< 001	< 2 > 1	> 5	< 2 > 1	< 005 > 01
D. Enlarged left ventricle, elevated wedge pressure, heat						
C	79	113	44	6 94	3 1	2 57
2 hr	87 + 10 1	99 − 12 4	46 + 4 5	6 96 + 0 3	3 2 + 3 2	2 22 − 13 6 %
1 (C vs 2)	< 001	< 001	< 4 > 3	> 5	< 4 > 3	< 02 > 01
*Significance analyses of control Group A versus Groups B, C, and D**						
p (Controls vs B)	< 005 > 01	< 005 > 01	> 5	> 5	> 5	< 005 > 01
p (Controls vs C)	< 001	< 001 > 005	> 5	> 5	> 5	< 01 > 02
p (Controls vs D)	< 005 > 01	< 001 > 005	> 5	> 5	> 5	< 01 > 02

*The comparisons are between the final percentile changes in Group A versus those [illegible] the other groups (Fisher [illegible] test for groups of less than 30).
For key to abbreviations, see footnotes to Table I.

Table VI. Average data on arterial pCO_2

	Group A	*Group B*	*Group C*	*Group D*
Control	44	43	45	44
2 hr	43 − 2.2%	46 + 7.0%	49 + 8.9%	48 + 9.0%
p	< .4	< .001	< .001	< .001
p (A vs B,C,D)	—	< .001	< .001	< .001

normal flow of blood to the brain. The subjects in this study were free of clinically demonstrable mechanical obstructions to cerebral arterial flow. However, on the basis of evidence available in the literature,[4] there is no reason to suspect that the findings would differ in patients with cerebral arteriosclerosis.

Summary

The effect of an exposure to a warm and dry environment (98° F. and 40 per cent relative humidity) for 2 hours on the cerebral blood flow was investigated in resting normal subjects as well as in patients with diseased left ventricles.

The reduced perfusion pressure caused by the ensuing reduction in the systemic arterial pressure was attended by a maintenance of the cerebral blood flow at control levels. This was due to a significant reduction in the cerebral arterial resistance caused, at least in part, by a significant elevation of the arterial pCO_2.

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Pulmonary pressor action of l norepinephrine and angiotensin

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In hemodynamic studies of experimental animals and man, both angiotensin and norepinephrine increase systemic vascular resistance, presumably by constricting arterioles or small arteries.[1] However, the actions of these two drugs are not the same in all parts of the circulation. Norepinephrine is a systemic venoconstrictor, whereas angiotensin has less effect upon veins.[2] In the coronary circulation, we have found that angiotensin produced a striking increase in coronary vascular resistance, whereas norepinephrine had no similar action. Thus, it seemed desirable to study the effects of these two agents upon the pulmonary circulation, and to compare their action with that of similar amounts of serotonin, which is generally acknowledged to be a pulmonary vasoconstrictor.

Study of the action of a pharmacologic agent upon the pulmonary circulation requires control of several variables, which, when uncontrolled or not measured, may lead to misinterpretation of changes in flow and pressure. Cardiac output should be steady, since it is known that an increase in pulmonary blood flow tends to decrease pulmonary vascular resistance and a decrease in pulmonary blood flow tends to increase pulmonary vascular resistance.[4] Left atrial pressure should be constant, since an increase in left atrial pressure tends to decrease pulmonary vascular resistance.[5] Bronchoconstrictor or bronchodilator effects of the drug under study should be eliminated or measured.[6] An agent which increases systemic blood pressure may cause a shift of blood into the lungs through bronchial collateral circulation; however, such changes are probably small when the bronchial collateral vessels are of normal size.[7] Variations in blood pH and in ventilation should be minimized or avoided.[7]

Accordingly, the pulmonary vascular effects of the three drugs employed in this study were made in such a way that pulmonary blood flow, left atrial pressure, ventilation, and systemic arterial pressure remained within certain limits. Intratracheal pressures were measured, and some studies were carried out during suspended respiration.

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Methods

The studies to be described were made upon mongrel dogs, anesthetized with pentobarbital sodium 30 mg per kilogram intravenously Instead of pentobarbital 3 animals received morphine sulfate 5 mg per kilogram intramuscularly and chloralose 66 89 and 129 mg per kilogram intravenously All animals received 5 mg of heparin per kilogram intravenously The chest was opened and respiration with 100 per cent oxygen was maintained by a Harvard respirator set at 16 strokes per minute with a stroke volume of 250 to 300 ml as required to obtain adequate lung inflation The respiratory rate and volume were maintained constant throughout each experiment. The superior vena cava was cannulated after ligation of the azygos vein and the effluent blood drained into a heated jacket reservoir The proximal inferior vena cava was cannulated and blood from the reservoir was pumped at a constant rate into the right atrium through this cannula by means of a roller pump Then the inferior vena cava was cannulated distally and its effluent drained into the same reservoir The coronary sinus was not ligated The dead space of the reservoir system was filled with fresh heparinized donor blood. All donor blood was pooled before the beginning of an experiment. Blood temperature was monitored constantly with a thermistor and was maintained at 37.5 ± 0 5°C Blood pH was measured at 37°C with a Beckman expanded-scale pH meter At intervals of 15 to 30 minutes, 150 ml of 2.5 per cent sodium bicarbonate was added to the perfused blood No drug studies were carried out until circulatory pressures had stabilized after the addition of sodium bicarbonate Simultaneously pressures were measured in the pulmonary artery left atrium trachea, and aorta by means of Statham transducers and a direct writing Sanborn Poly Viso oscillograph Pulmonary arterial pressure was recorded in most experiments so that a change in pressure of 1 mm Hg caused a paper deflection of 5 mm In the remainder a change in pressure of 1 mm caused a deflection of 2 mm

Group 1 Continuous drug infusion during constant pulmonary blood flow without control of left atrial pressure Pressures were measured during a control period and during continuous intrapulmonary infusion of angiotensin 10 µg per minute l-norepinephrine base 10 and 20 µg per minute and serotonin creatinine sulfate 300 µg per minute Pressures were measured until subsidence of drug effect These dosages of l norepinephrine and angiotensin were chosen because a systemic pressor effect is ordinarily produced by these amounts. The dosage of serotonin chosen lay in the range found by Rudolph and Paul[8] to produce effects upon the pulmonary circulation Each drug was infused in 1 1 to 3 9 ml of normal saline per minute Blood flows were measured during and after drug infusion by timed collection of superior and inferior vena caval flow into a graduated cylinder Control studies were made by infusing 3 9 ml of physiologic saline per minute Satisfactory studies were made in 7 animals, which weighed from 10 9 to 17.3 kilograms and which had pulmonary flows of 92 to 115 ml per kilogram per minute

Group 2 Single rapid injections of drug with controlled left atrial pressure The animals were initially prepared as described in Group 1 In addition constant blood flow to the head was maintained by cannulation of both common carotid arteries, and the lower part of the body and the lower extremities were perfused by cannulation of the descending thoracic aorta through the left subclavian artery The pulmonary venous return was drained from the apex of the left ventricle through an end-and-side hole cannula into a reservoir set at normal left atrial level (R_3, Fig 1) From this reservoir blood was drained into a heated jacket reservoir (R_4, Fig 1) whence it was pumped at a constant rate identical to the pulmonary perfusion rate into the descending aorta and carotid arteries (Fig 1) The aortic arch and right subclavian artery were ligated and ventricular fibrillation was induced by electrical stimulation of the ventricles This step was necessary to obviate changes in left atrial pressure induced by inotropic effects of the injected drugs. Circulation to the head was maintained at all times and carotid sinus reflexes were determined at the end of each experiment

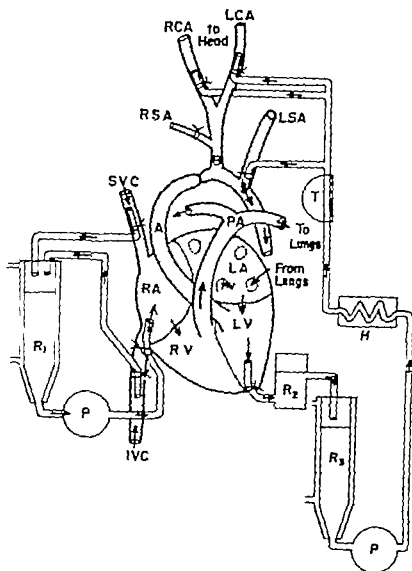


Fig. 1. Diagram showing arrangement for constant flow perfusion of lungs and systemic circulation. *SVC*, Superior vena cava; *IVC*, Inferior vena cava; *R*, *R2*, *R3*, Blood reservoirs; *P*, Roller pump; *T*, Thermistor; *H*, Heated coil; *LSA*, Left subclavian artery; *PA*, Pulmonary artery; *PV*, Pulmonary veins; *RCA*, *LCA*, Right and left carotid arteries; *LSA*, *RSA*, Left and right subclavian arteries; *A*, Aorta; *B*, Brachiocephalic artery.

Each animal received serial rapid single injections of l-norepinephrine base and of angiotensin 10, 20, 50, and 100 µg, and of serotonin creatinine sulfate 20, 40, 100, and 200 µg. The weight of serotonin creatinine sulfate was twice that of angiotensin and l-norepinephrine because only 45 per cent of the creatinine sulfate compound is composed of serotonin base. The drug solutions in volumes of 0.4 to 2 ml. and warmed to 37°C. were injected into the outflow tract of the right ventricle just inferior to the pulmonary valve. The order of drug injections was randomized. Immediately after the injection of a drug into the pulmonary artery, the pulmonary venous return was prevented from entering the systemic circulation by collection of the blood in a separate container and simultaneous replacement with donor blood. Thus, any direct effect of the drug upon the systemic circulation was obviated *until* after the peak change in pulmonary arterial pressure had taken place. After the maxi

mum pulmonary pressor response the collection was terminated and a small amount of the injected drug then entered the systemic circulation. Each animal received a control single rapid injection of 2 ml of physiologic saline at 37°C It was necessary to be certain that the changes in pulmonary pressure which followed the drugs were not related to an effect of the drug upon the fibrillating myocardium. In one animal (No 291) the main pulmonary artery was cannulated through the outflow tract of the right ventricle and all systemic venous blood completely bypassed the right heart. In this animal drugs were injected directly into the main pulmonary artery and the results were similar to those in the other animals. Blood pH was measured at the beginning and end of the series of injections of each individual drug Studies were carried out in 9 animals weighing from 9 1 to 17 kilograms. The results were discarded in one because blood pH had fallen to 7 10 at the end of the experiment. Pulmonary flows were measured before during and after each injection of drug by timed collection of the pulmonary venous return in a graduated cylinder In these animals the pulmonary flow rates were 75 to 100 ml. per kilogram per minute. In 3 additional animals the effect of serotonin creatinine sulfate was observed after the hematocrit was lowered to 2, 14 and 22 per cent by 6 per cent isosmotic dextran exchange

Group 3 Studies of serotonin during suspended respiration The 3 animals in this group were prepared as in Group 1 except that the blood draining from the superior and inferior venae cavae was oxygenated in a disposable bubble oxygenator before being pumped at a constant rate into the right atrium In these animals the effect of single injections of 150 or 300 μg of serotonin creatinine sulfate upon pulmonary vascular resistance was studied while respirations were suspended by disconnecting the respirator This was done in order to minimize the bronchomotor effects of serotonin

Results

Group 1 Constant drug infusions into the pulmonary arteries of animals with controlled venous return to the right heart Infusions of angiotensin 10 μg per minute and l norepinephrine 10 and 20 μg per minute produced no consistent effect upon pulmonary vascular resistance (Table I) Blood pH values obtained at the time of the infusions of l norepinephrine or within 4 minutes are shown in Table I Infusion of serotonin 300 μg per minute, resulted in consistent moderate increases in pulmonary vascular resistance (Table I) With infusion of 3 9 ml. of saline per minute pulmonary vascular resistance remained unchanged or fell slightly The ratios of resistance during infusion of saline to control resistance were from 0 96 to 1 00 Aortic pressure rose in each of 6 animals which received angiotensin 10 μg per minute Control mean aortic pressure was 110 mm Hg during infusion of angiotensin, mean aortic pressure was 147 mm Hg Aortic pressure also rose in each of 7 animals which received l norepinephrine, 10 μg per minute Control mean aortic pressure was 104 mm Hg during infusion of l norepinephrine mean aortic pressure was 113 mm Hg Only 1 of 5 animals demonstrated a rise in aortic pressure during infusion of serotonin creatinine sulfate 300 μg per minute Intratracheal pressure showed no change in animals Nos. 227 228 and 229 during infusion of serotonin In animal No 232 intratracheal pressure rose 13 2 mm Hg and in animal No 235 intratracheal pressure rose 14 4 mm Hg during infusion of serotonin Intratracheal pressure showed no change after angiotensin Infusion of l-norepinephrine 10 μg per minute, produced no change in intratracheal pressure in 5 of 8 animals. In 3 there were small increases of 0 5 0 9 and 2.5 mm Hg

Group 2 Serial rapid single injections of drug into the outflow tract of the right ventricle of animals with cardiac arrest and constant pulmonary and systemic blood flow Blood pH was maintained at 7 30 or above in all animals, except Nos. 286 and 287 in which values as low as 7 23 were obtained

PULMONARY VASCULAR RESISTANCE The results in 8 animals are shown in detail in Tables II III and IV During the control injections of 2 0 ml of physiologic saline changes in pulmonary arterial pressure and pulmonary vascular resistance

*Table I. Effect of continuous infusions of angiotensin, l-norepinephrine, and serotonin upon pulmonary vascular resistance**

Dog No.	*Angiotensin (10 μg/min.)*		*Serotonin (300 μg/min.)*		*l-Norepinephrine (10 μg/min.)*		*l-Norepinephrine (20 μg/min.)*		*Blood pH*
	Control resistance	*Ratio to control resistance*	*Control resistance*	*Ratio to control resistance*	*Control resistance*	*Ratio to control resistance*	*Control resistance*	*Ratio to control resistance*	
226					8 0	0 99	7 9	0 94	7 48
227	16 7	0 95			17 6	0 98			7 12
228	1 5	1 05	10 1	1 55	15 0	0 99	14 8	0 97	
229	8 7	1 16	8 3	1 12	9 2	1 00	9 3	1 11	7 30
230	10 9	1 00	10 5	1 18	10 8	1 01			7 34
232	8 5	0 96	8 7	1 10	11 0	1 04			7 42
233	18 3	0 93	14 0	1 23	14 2	1 04			7 13

*Expressed as $\frac{PA - LA}{Q}$ where PA = mean pulmonary arterial pressure, mm. Hg, LA = mean left atrial pressure, mm. Hg, and Q = pulmonary blood flow in liters per minute.

*Table II. Effect of l-norepinephrine upon pulmonary vascular resistance**

Dog No.	Weight (Kg.)	*Control*				*Injection of 2 ml. of saline*		*l-Norepinephrine 10 μg*		*20 μg*		*50 μg*		*100 μg*		*Final pH*	*l-Norepinephrine (10 μg)*
		pH	*PAP*	*LAP*	*PVR*	*PAP ratio*	*PVR ratio*	*PAP ratio*	*PVR ratio*	*PAP ratio*	*PVR ratio*	*PAP ratio*	*PVR ratio*	*PAP ratio*	*PVR ratio*		*AP ratio*
286	17 0	7.29	23.5	3.3	10 9	1.00	1.00	1.02	1.05	1.05	1.09	1 10	1 12	1 12	1 14	7.23	
287	12.7	7.36	18 3	0.5	19 1	0.99	0.98	1.08	1 07	1 17	1 18	1.23	1.22	1.21	1 18	7.36	
288	9 1	7.34	21.6	6 0	16 9	0.97	0 97	1.05	1.06	1.08	1.09	1 11	1.10	1 19	1.25	7.34	1.33
289	15.0	7.38	19.8	6.8	8.7	0.98	0.95	1 03	1.03	1.06	1 10	1 06	1 10	1 10	1 16	7.39	1 47
291	14 0	7 40	23 9	4.3	13 9	0.97	0.93	1 04	1.04	1.07	1 13	1 13	1 17	1 18	1.26	7.35	1.61
292	13.0	7 41	17 1	0 9	12.3	0.99	1.01	1.05	1.06	1 11	1 12	1.18	1.20	1 15	1 15	7 43	1.57
293	10.5	7.33	17 7	1 8	15 1	0 98	0.98	1.05	1.05	1 10	1 16	1 19	1.27	1.27	1.30	7.33	1.34
294	14.0	7.39	16.3	7.3	8.2	1.01	1.00	1 06	1 08	1 12	1 17	1.22	1.23	1.22	1.26	7.36	1.33
Mean								1.05	1 06	1 10	1 13	1 15	1 15	1 18	1.21		1 44

*Pulmonary vascular resistance is calculated as shown in footnote to Table I.

PAP: Mean pulmonary arterial pressure, mm. Hg. *LAP*: Mean left atrial pressure, mm. Hg. *PVR*: Pulmonary vascular resistance. *PAP ratio*: Represents quotient of pulmonary arterial pressure after drug divided by control pressure. *PVR ratio*: Represents quotient of pulmonary vascular resistance after drug divided by control resistance. *AP ratio*: represents quotient of aortic pressure after injection of drug into the aorta divided by control pressure.

were small (Table II). Changes in pulmonary arterial pressure ranged from a 3 per cent decrease to a 1 per cent increase. Changes in pulmonary vascular resistance were from a 7 per cent decrease to a 1 per cent increase.

During drug injection, pulmonary blood flow was unchanged in the majority of experiments. However, in several studies, pulmonary blood flow increased or decreased slightly, but always no more than 5 per cent, except for a decrease of 7 per cent after 100 µg of serotonin in Dog No. 287.

L-norepinephrine, 10 µg, produced a slight but definite increase in pulmonary vascular resistance in each animal, the mean increase being 6 per cent (Table II).

Table III. Effect of angiotensin upon pulmonary vascular resistance

Dog No.	Control				Angiotensin 10 µg		Angiotensin 20 µg		Angiotensin 50 µg		Angiotensin 100 µg		Final pH	Angiotensin (10 µg)
	pH	PAP	LAP	PVR	PAP ratio	PVR ratio	PAP ratio	PVR ratio	PAP ratio	PVR ratio	PAP ratio	PVR ratio		AP ratio
286	7.23	21.3	3.2	10.1	1.08	1.04	1.07	1.01	1.07	1.07	1.08	1.08	7.30	
287	7.37	18.8	0.9	19.1	1.10	1.06	1.08	1.08	1.11	1.12	1.14	1.15	7.36	
288	7.34	20.0	5.7	15.9	1.03	1.03	1.03	1.08	1.07	1.11	1.05	1.04	7.36	1.21
289	7.39	20.8	6.8	9.3			1.02	1.04	1.08	1.12	1.18	1.23	7.32	1.11
291	7.47	22.7	1.0	15.5	1.06	1.05	1.04	1.04	1.11	1.10	1.15	1.17	7.37	1.18
292	7.39	15.7	1.1	11.3	1.06	1.04	1.14	1.15	1.28	1.34	1.37	1.43	7.41	1.34
293	7.41	19.9	1.6	18.0	1.07	1.07	1.10	1.04	1.23	1.26	1.17	1.21	7.35	1.24
294	7.40	15.1	7.6	5.6	1.01	1.02	1.07	1.13	1.15	1.45	1.20	1.47	7.40	1.29
Mean					1.06	1.04	1.07	1.07	1.14	1.20	1.26	1.23		1.23

For key to abbreviations see footnotes to Table II.

Table IV. Effect of serotonin upon pulmonary vascular resistance

Dog No.	Control				Serotonin 20 µg		Serotonin 40 µg		Serotonin 100 µg		Serotonin 200 µg		Final pH	Serotonin (20 µg)
	pH	PAP	LAP	PVR	PAP ratio	PVR ratio	PAP ratio	PVR ratio	PAP ratio	PVR ratio	PAP ratio	PVR ratio		AP ratio
286	7.30	23.5	4.5	10.6	1.06	1.11	1.12	1.11	1.16	1.20	1.27	1.35	7.30	
287	7.36	17.6	0.4	18.9	1.12	1.10	1.09	1.08	1.28	1.42	1.37	1.23	7.23	
288	7.34	20.2	5.9	15.9	1.10	1.13	1.10	1.13	1.11	1.15	1.33	1.43	7.41	1.00
289	7.32	20.2	6.1	9.5	1.03	1.06	1.06	1.06	1.02	1.05	1.19	1.26	7.34	1.16
291	7.35	22.3	5.0	12.3	1.11	1.10	1.12	1.15	1.35	1.42	1.43	1.57	7.34	1.15
292	7.43	16.4	1.8	11.3	1.05	1.09	1.13	1.15	1.20	1.23	1.31	1.33	7.39	1.10
293	7.35	18.0	1.3	16.2	1.12	1.12	1.13	1.17	1.26	1.26	1.38	1.43	7.53	1.06
294	7.31	16.9	7.0	6.9	1.01	1.01	1.07	1.18	1.14	1.30	1.23	1.49	7.40	1.00
Mean					1.06	1.09	1.10	1.13	1.19	1.26	1.31	1.39		1.08

For key to abbreviations see footnotes to Table II.

With larger doses, the mean rise increased and was 21 per cent after 100 μg (Table II Fig 2) However in individual animals, the increase in resistance was not always greater after 100 μg than after 50 μg (Table II Fig 3)

The mean rise in aortic pressure after 10 μg of l norepinephrine injected into the aorta was 33 per cent and always exceeded the *percentage increment* in pulmonary resistance for the same dose Aortic and left atrial pressures did not change when the drug was injected into the right ventricle and the pulmonary venous return collected

With angiotensin the changes in pulmonary resistance were comparable to those observed after l norepinephrine

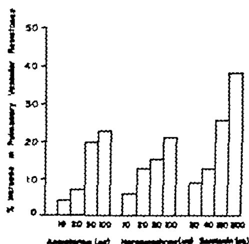


Fig 2 Comparison of mean percentage changes in pulmonary vascular resistance produced in 8 animals by single injections of l norepinephrine, angiotensin and serotonin creatinine sulfate

Fig 3 Effect of injections of l-norepinephrine 10, 20 50, and 100 μg, upon pulmonary vascular resistance of a 13-kilogram dog No. 292 Pulmonary flow was constant at 100 per ml. kilogram per minute The rise in pulmonary arterial pressure was somewhat less after 100 μg than after 50 μg Note the constant left atrial pressure After the peak pulmonary pressor effect there is a small rise in aortic pressure as some of the drug was permitted to enter the systemic circulation. See Table II

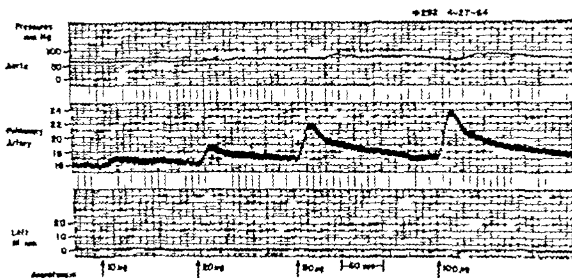


Fig. 4. Effect of injections of angiotensin 10, 20, 50 and 100 μg, upon pulmonary vascular resistances of Dog No. 292 (same dog as in Fig. 3). Pulmonary blood flow was 100 ml. per kilogram per minute. Note the constant left atrial pressure. See Table III. After 50 and 100 μg of the drug there was some rise in aortic pressure after the peak pulmonary pressor effect, as some of the drug was permitted to enter the systemic circulation.

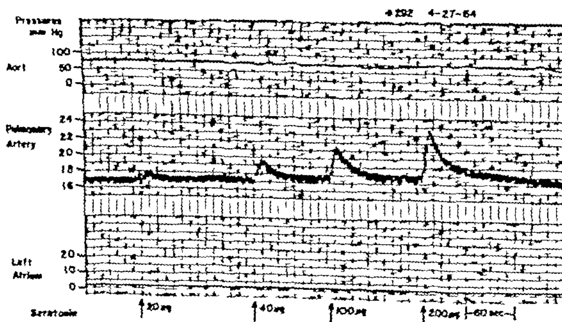


Fig. 3. Effect of injections of serotonin creatinine sulfate, 20, 40, 100 and 200 μg, upon pulmonary vascular resistance of Dog No. 292 (same dog as in Figs. 3 and 4). Pulmonary blood flow was 100 ml. per kilogram per minute. Left atrial and aortic pressures were essentially unchanged. See Table IV.

(Table III Fig 2) With doses of 10 μg pulmonary vascular resistance increased in each animal but averaged only 4 per cent After 100 μg the mean increment in resistance was 23 per cent Aortic and left atrial pressures were essentially unchanged after angiotensin when the pulmonary venous return was collected so as to prevent entrance of the drug into the systemic circulation (Fig 4) When 10 μg of angiotensin was injected into the aorta the mean increase in systemic resistance was 23 per cent and always exceeded the percentage increase in pulmonary resistance for the same dose

With serotonin the mean increment in pulmonary vascular resistance exceeded that with comparable amounts of angiotensin and l norepinephrine at each dose level (Figs 2 and 3 Table IV) After 20 μg of serotonin creatinine sulfate comparable to 10 μg of *l* norepinephrine or angiotensin the mean rise in pulmonary resistance was 9 per cent, and was 39 per cent after 200 μg of serotonin creatinine sulfate an amount comparable to 100 μg of angiotensin or l norepinephrine The mean rise in systemic resistance was 8 per cent after 20 μg of serotonin was injected into the aorta. In some animals the increment in pulmonary vascular resistance after 20 μg of serotonin into the right ventricle exceeded the per cent rise in systemic resistance when 20 μg of the drug was injected into the aorta

In the 3 animals which were given dextran to lower the hematocrit pulmonary vascular resistance increased 30 per cent after 300 μg of serotonin in one 35 per cent after 600 μg of serotonin in a second and 36 per cent after 200 μg in the third whose hematocrit was only 2 per cent

PULMONARY ARTERIAL PRESSURE. Control mean pulmonary arterial pressures were 15 1 to 23 9 mm Hg (Tables II III and IV) After 10 μg of l norepinephrine, the maximum increase in pulmonary arterial pressure was 1 4 mm Hg with 100 μg the pressure rose as much as 5 mm Hg After 10 μg of angiotensin, the maximum increase was 1 9 mm Hg after 100 μg of angiotensin the maximum rise was 6.3 mm. Hg After 20 μg of serotonin creatinine sulfate, the maximum rise in pulmonary arterial pressure was 2 5 mm Hg after 200 μg the maximum rise was 9 9 mm Hg

LEFT ATRIAL PRESSURE Control left atrial pressures were 0 4 to 7 6 mm Hg In only one animal did the left atrial pressure show a change in excess of 0 5 mm Hg after drug injections. In animal No 288 left atrial pressure rose 0 9 mm Hg after 50 μg of l norepinephrine and 1 4 mm Hg after 100 μg of l norepinephrine. There was also a rise of 0 8 mm Hg after 200 μg of serotonin In all other studies, left atrial pressure varied no more than 0.5 mm Hg and was considered to be essentially constant

TRACHEAL PRESSURE. Tracheal pressure was recorded in 7 animals during the administration of serotonin and in 6 animals during the administration of angiotensin and l-norepinephrine. Control end inspiratory pressures were 7 5 to 20 1 mm Hg After drug administration only one animal No 291 demonstrated a change in end-inspiratory pressure in excess of 1 mm Hg In this animal the pressure rose 1 9 mm Hg after 100 μg of angiotensin and 1 8 mm Hg after 200 μg of serotonin creatinine sulfate.

AORTIC PRESSURE Control aortic mean pressures were 60 to 153 mm Hg At the time of peak pressure effect on the pulmonary artery after injection into the right ventricle there was in no instance a measurable increase in aortic pressure One animal No 291 demonstrated a decrease of 15 mm Hg in aortic pressure at the time of peak rise in pulmonary pressure after 20 μg of angiotensin was injected into the right ventricle In the same animal, there was a decline of 10 mm. Hg in aortic pressure after injection of 100 μg of angiotensin into the right ventricle. In Dog No. 292 there was a fall of 10 mm Hg in aortic pressure after 100 μg of angiotensin Also Dog No 286 showed a fall of 5 mm Hg in aortic pressure after 100 μg of angiotensin into the right ventricle and Dog No. 288 demonstrated a decline of 5 mm Hg in aortic pressure after 200 μg of serotonin into the right ventricle

Group 3 Constant return of oxygenated venous blood to the right heart with suspended respiration In these animals injection of 300 or 600 μg of serotonin into the pulmonary artery produced a much greater

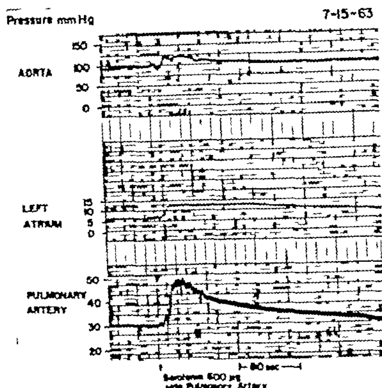


Fig. 6. Effect of 600 μg of serotonin creatinine sulfate upon the pulmonary arterial and left atrial pressures in an 11.4-kilogram dog with suspended respiration and constant pulmonary flow of oxygenated blood. Pulmonary blood flow was 75 cc. per kilogram per minute. After serotonin, the left atrial pressure rose from 6.5 to 13 mm. Hg, and pulmonary arterial pressure rose from 30.5 to 49.5 mm. Hg. Pulmonary vascular resistance increased from 30 to 48 units.

increase in pulmonary arterial mean pressure than in left atrial mean pressure, and thus, an increase in pulmonary vascular resistance (Fig. 6). In this dog, No. 244, control pulmonary vascular resistance was 30 units and increased to 48 units during the peak effect of serotonin.

Discussion

In order to demonstrate a pulmonary vascular action of drugs, it is necessary to employ rather large doses because of the relative insensitivity of the lung vessels to drugs. Previous studies in intact animals and in man[3,4] and in open-chest animals[1] have failed to demonstrate a change in pulmonary vascular resistance after angiotensin. However, we have demonstrated with moderate and high doses of angiotensin a pulmonary vascular effect approximately two thirds as great as that with serotonin. The doses of angiotensin used in our study, however, are larger in proportion to body weight than one would expect to employ in a clinical study.

Eckert and Rose[11] studied the effects of 0.5 to 6 mg. of angiotensin upon pulmonary vascular resistance in animals and found *no change in pulmonary pressure or vascular resistance*. However, these investigators were using an earlier preparation of angiotensin furnished by Dr. I. S. Page with a potency of 32 units per milligram. Commercial lots of angiotensin II have been found to have 7.2 to 11.1 units per microgram.[12] Therefore, the angiotensin employed by Eckert and Rose had approximately $\frac{1}{300}$ the potency of the preparation used in our study. Thus, the highest dose used by Eckert and Rose was equivalent to 20 μg of the present preparation. At

this dose level, we found an average increase in pulmonary vascular resistance of only 7 per cent with angiotensin. In a later publication, Rose and associates[2] found no increase in pulmonary vascular resistance after systemic pressor doses of angiotensin. Our observations are not necessarily in conflict with these studies since we found no change in pulmonary vascular resistance with a continuous infusion of angiotensin, 10 μg per minute, which produced a striking systemic pressor effect. Yu and co-workers[9] observed a rise in pulmonary arterial pressure during infusion of angiotensin in man and in dogs. These investigators concluded that the rise in pulmonary pressure was secondary to an increase in left ventricular diastolic pressure. Chimoskey and associates[10] found an increase in pulmonary arterial pressure after single doses of 2.0 μg per kilogram of synthetic angiotensin II. These authors concluded that the pulmonary pressor effect was secondary to the systemic pressor effect. However, left atrial pressure and pulmonary flow were not controlled in this study, and it would have been difficult to be certain of a separate effect of angiotensin upon the pulmonary blood vessels. It is reasonable to conclude that changes in pulmonary pressure with ordinary systemic pressor doses of angiotensin are predominantly secondary to systemic and cardiac effects.[3] However, our present study reveals that if systemic and cardiac effects are eliminated, a small pulmonary vascular action can be demonstrated with systemic pressor doses of angiotensin.

Numerous studies of serotonin have established with reasonable certainty that it increases pulmonary vascular resistance.[1,13] However, in many investigations, questions may be raised because the drug increased pulmonary blood flow[8] or pulmonary blood flow was very small[14] or denervated preparations were used,[14,15] or left atrial pressure was not measured or bronchoconstriction was not excluded.[8] All of these influence pulmonary resistance. It has been stated that as little as 50 μg of serotonin intravenously in dogs may produce whitish thrombi in the pulmonary arteries and that the drug may increase pulmonary vascular resistance in this way,[8] at least in part.[16] Furthermore, Swank and associates[17] have demonstrated the aggregation of blood elements in heparinized blood after the addition of serotonin. Obstruction of small pulmonary blood vessels by this mechanism might cause an increase in calculated resistance.

The present study resolves many of these problems, in that increased pulmonary vascular resistance was clearly shown when pulmonary blood flow was maintained constant at physiologic rates near 100 ml. per kilogram per minute and left atrial pressure did not change. A possible pulmonary vascular effect of bronchoconstriction was reduced by studies made during suspended respiration. In addition, reflex effects from the systemic circulation or increased bronchial flow were avoided in the present studies. Our studies are open to two criticisms. Most animals were studied under pentobarbital anesthesia and it may be assumed that reflex responses were impaired. However, some rise in blood pressure in response to carotid artery occlusion could be demonstrated in nearly all preparations. The possibility of thrombus formation or blood cell agglutination was not entirely excluded, although vascular resistances returned to control values 90 to 240 seconds after serotonin. Also, in some animals, little change in systemic pressure was seen after serotonin was injected into the aorta. Furthermore, increased pulmonary vascular resistance to serotonin was observed in 3 animals after their hematocrits had been reduced to 2, 14, and 22 per cent by partial exchange of dextran for blood.

The response of the pulmonary vascular bed to norepinephrine has been in question. In man, we were unable to demonstrate increased pulmonary vascular resistance after l-norepinephrine, 0.2 to 0.4 μg per kilogram per minute;[11] however, an increase in pulmonary "wedge" pressure may have [illegible]ed a [illegible] to pulmonary [illegible] ve found by his [illegible] h[illegible] with regulat[illegible] h[illegible] nephri[illegible] pul[illegible] resistanc[illegible] er[illegible] vascular [illegible] [illegible]pir[illegible] p[illegible] in[illegible]

mia may have influenced the results. Recently Goldring and associates[22] found no rise in pulmonary vascular resistance after a single injection of 0.4 to 0.8 μg of norepinephrine in patients studied at thoracotomy.[22] Bousvaros[23] found a temporary increase in the pulmonary arterial–left atrial pressure gradient in 9 patients given 30 to 50 μg of norepinephrine intravenously in 40 seconds. However, a transient increase in pulmonary blood flow may have accounted for these results. Ring and co-workers[22] found that during infusion of norepinephrine there was a decrease in the movement of microspheres less than 5 micra in diameter across the pulmonary vascular bed of dogs. This observation was interpreted as suggesting constriction of small pulmonary arteries. It is known that the low pH of extracellular fluid tends to impair norepinephrine-induced contraction of arterial smooth muscle.[24] In our studies blood pH was not sufficiently abnormal to mitigate a vasoconstrictive action of this drug. Our present study shows small and consistent effects of l-norepinephrine upon pulmonary vascular resistance in single doses of 10 to 100 μg. This observation does not necessarily conflict with the studies of Goldring and associates[22] who employed much smaller amounts of norepinephrine.

The present study indicates that a given weight of angiotensin has approximately the same effect upon the pulmonary vascular bed as does l norepinephrine and the action of each is approximately two thirds as great as that of a comparable amount of serotonin. The molecular weight of angiotensin is approximately six times as great as that of serotonin and l-norepinephrine. Thus, on a molar basis, angiotensin has a more potent effect than either agent upon the pulmonary vascular bed. The actions of angiotensin and of l-norepinephrine upon the pulmonary vascular bed appear to differ little in degree, in contrast to their different effects upon the systemic veins and the coronary vascular bed. However, the site of action of the several drugs in the pulmonary vascular bed may well be different. It should be emphasized that no pulmonary vascular effect of angiotensin could be demonstrated at dose levels likely to be used in the treatment of shock (0.58 to 0.91 μg per kilogram per minute).

Summary and conclusions

In animals with constant venous return to the right heart, angiotensin 10 μg per minute and l-norepinephrine 10 and 20 μg per minute produced no increase in pulmonary vascular resistance. Serotonin creatinine sulfate 300 μg per minute, consistently produced a moderate increase in pulmonary vascular resistance.

In animals in which left atrial pressure and pulmonary blood flow were controlled and in which systemic and cardiac effects were obviated, single doses of 10, 20, 50 and 100 μg of l-norepinephrine and of angiotensin each produced consistent and comparable increases in pulmonary vascular resistance. These increments averaged 6 per cent for 10 μg of l-norepinephrine, 4 per cent for 10 μg of angiotensin, 21 per cent for 100 μg of l norepinephrine and 23 per cent for 100 μg of angiotensin. These changes were approximately two thirds as great as those produced by comparable weights of serotonin. On a molar basis, angiotensin was found to be a more potent drug than serotonin in its effect upon pulmonary vascular resistance. The changes in pulmonary vascular resistance in these animals were unrelated to changes in left atrial pressure or to systemic drug effects. Pulmonary vascular resistance increased significantly after serotonin in animals with suspended respiration; thus, bronchomotor effects did not seem to be a major contributing factor to the increase in pulmonary vascular resistance. The pressor effects of a given weight of angiotensin and l-norepinephrine upon the pulmonary vascular bed appear to be similar in degree. Serotonin was the only drug of the three to increase pulmonary vascular resistance more than did a separate injection of the same dose increase systemic resistance.

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Compensation of arterial insufficiency by augmenting the circulation with intermittent compression of the limbs

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The recent description in this country and in Germany of the favorable effects of a medical massage suit in the treatment of conditions of severe chronic arterial insufficiency has prompted the accompanying study of the mechanism of this device. Introduced as an experimental item in 1955,[1] suitable modified equipment is now commercially available.† It consists of an inflatable legging that simulates "walking" by intermittently and briefly compressing the lower leg for a variable preselected period and then releasing the pressure for a rest phase, the duration of which is also selected. The inflation is achieved by means of an electrically operated portable pump and timer.† The original observations of Beecher, Field, and Krogh[2] established that venous pressure at the ankle is grossly reduced by walking actions. This reduction in pressure occurs because the valves in the veins prevent refilling from above. Hence, the veins will be kept empty as long as the pumping rate is sufficiently rapid to remove all the blood that arrives from the capillary bed. The rate of flow of blood through the foot determines the rhythm necessary for effective reduction in pressure.[3] When a normal subject is hot, the temperature-regulating shunt vessels of the skin of the foot are dilated. Flow through the part is enormously enhanced, greatly exceeding the nutritional demands of the tissue, and the veins fill up again in a few seconds after they have been emptied by a contraction of the leg muscles. It is necessary to evert and relax the pressure on the veins with a rhythm of one per second in order to achieve an effective reduction in pressure. When the foot is cold and the shunts are closed, or in cases of arterial insufficiency in which the total flow capability is greatly reduced, a much slower rhythm of one to two times a minute will suffice.

The use of a massage pump will maintain venous pressure in the extremities of a man in the upright posture at levels near normal for recumbency and well below those leading to the formation of edema, despite the great potential increment because the foot is now so far below the level of the heart.[1] At the same time, the pres-

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sure in the arteries of the foot will increase by the amount of this distance from heart to foot. In the human adult seated erect in a chair the change in the arteriovenous pressure differential will be the order of 30 to 40 mm Hg.

Such an increase in the driving pressure not unexpectedly leads to an increase in the total flow of blood through the part. Thus in 1957 Allwood[4] established that intermittent compression of a normal leg of a subject in the upright seated posture increases the mean total flow of blood by approximately 60 per cent. He demonstrated this with a plethysmographic technique using a capacitance manometer. In diseased limbs an increase of 30 per cent was observed. Loane[5] later confirmed these results. Using both calorimetric heat flow and plethysmographic methods he established that the improvement in blood flow was at least as great as the increase in perfusion pressure, i.e., approximately 40 per cent. Thus there is satisfactory evidence of an improved total flow of blood by this approach to mechanical massage which takes advantage of the gravity effect.

Studies were initiated to see whether upon application of intermittent pressure to the calf of the dependent leg there was any evidence not merely of an increased total flow of blood in the part but also of an improved rate of removal of a labeled tracer introduced into the tissues. Kety has shown [6] and subsequent work has fully confirmed that a diffusible tracer material such as Na^{24} or I^{131} [7] that simulates a natural metabolite can be used to estimate the effectiveness of the circulation through the tissues. Indeed, such a measurement is vital to permit a distinction between the nutritional circulation and high flow functional bypasses which Hyman suggests are to be found in muscle as well as in skin.[8]

The physiologic effectiveness of a device proposed to improve the circulation in arterial insufficiency is expressed in terms of the improvement of the total ability to remove (and to supply) freely diffusible substances. This is measured by the classic tissue clearance technique. As Kety pointed out in his original paper, the strength of this technique is that it evaluates not only the volume flow of blood but also other concomitant changes.[6] These include the opening up of closed capillaries with consequent decreases in diffusion distance and increases in filtration and reabsorption by the capillary bed.

Methods

Twelve normal subjects were employed. All were healthy males between the ages of 25 and 50. In addition, 10 diseased subjects were employed. Their condition ranged from very severe pregangrenous to minimal arterial disease as assessed clinically and by plethysmography which was used to determine pulse volume, blood pressure, blood flow, and peripheral resistance in the part. The upright seated posture was obtained by the use of a chair the seat of which was 60 cm. above the foot and in front of which was a desk attachment that permitted the subject to lean forward and rest some weight on his arms.

Massage was carried out by means of the previously mentioned medical massage unit that had a timer which permitted adjustment of on and off phases of the cycle. In the majority of these studies the period of inflation used for the normal subjects was approximately 3 to 5 seconds and the off period was 15 to 20 seconds. At the moment at which the peak pressure of 60-100 mm Hg was attained, the machine cut off. The pressure then rapidly fell to zero with the initiation of the rest cycle. In this way the leg was submitted to a minimum of pressure which might impose a resistance to the inflow of blood into the part and impair circulation to the skin. The actual massage garment consisted of an inflatable bag* which surrounded the leg, extending from the head of the fibula to the malleoli. A number of observations were also made with a simple cuff 8 cm. broad placed over the calf.

In these experimental studies the feet were left bare in order to permit the sampling of pressure and the injection of I^{131} in aqueous solution. Room temperature was maintained at approximately 72°F. and the subjects were clothed in a shirt

*An experimental item provided through the generosity of the David Clark Company, 360 Park Ave., Worcester 2, Mass.

and trousers. The temperature of the feet was monitored by means of a thermocouple and extremes of vasodilation and vasoconstriction with pallor and chilling were avoided. Liposodine* was administered in order to protect thyroid function. Administration of I131† in dosage of approximately 2 millicuries contained in 0.1 c.c. of fluid was given through a No. 27 needle. Care was taken to inject slowly in the attempt to prevent a local rise in pressure due to excessive accumulation. Two locations were employed. In one, the needle was inserted into the lateral aspect of the foot until the point was approximately 1 cm. beneath the surface of the skin and situated within the abductor muscle of the fifth toe. In the other, the needle was inserted into the fold of skin between the first and second digits. Counts were made over a period of 30 minutes by a scintillation counter‡ using a digital readout and recording on an ink writing recorder.§ The records were plotted on semilog paper and analyzed. The final result was taken as the "half time" or the time required for 50 per cent of the injected material to be removed. A control foot was always used as well as that which was being massaged. In subjects in whom more than one run was made, the control and experimental feet were alternated. Two types of study are presented. The normal subjects were seated in the chair for 3 hours. One calf was continuously massaged during this time; the other was not. Subjects were permitted to move both feet equally at intervals during this time. Movement was held down to a minimum compatible with comfort. They were not permitted to stand up. At the beginning of the third hour, while still being massaged, one foot was injected with I131. A 30-minute count was then taken in this foot and was followed by a count in the nonmassaged leg. The feet were injected at random, i.e., sometimes the first 30-minute count to be taken was on the control, sometimes it was on the massaged leg. Four subjects were also studied in the same way in the recumbent posture with the feet slightly above heart level.

The diseased patients were seated for only 1 hour with continuous pumping to one side before the first of the two injections of I131 was given. With another group of diseased subjects the pumping on the one side was continued for 1 hour. When it had been discontinued for 30 minutes, the first injection of I131 was given. The rate of removal was then contrasted in the control and in the previously massaged limbs.

Venous pressure

DIRECT MEASUREMENT. In a number of the normal subjects, venous pressure was measured directly by inserting a 20-gauge needle connected to a P23A Statham gauge into a vein of the dorsum of the foot. The pressure when the foot was immobile was contrasted with the mean steady level attained during massage.

INDIRECT MEASUREMENT. In those with diseased limbs, puncture of a vein was considered to be undesirable. A modification of the direct observation technique was employed by use of a Krogh, Turner, and Landis[4] capsule. The capsule was 2.5 cm. in diameter and was fabricated of Lucite, having a flat surface to permit observations of the subjacent veins. A flange 0.5 cm. broad permitted its attachment to the patient's skin by means of a punched-out disc of bilaterally adhesive plastic.* A tube leading off the side of the capsule permitted the application of a slow flow of air, the pressure of which could be adjusted until the vein under observation just collapsed. It was necessary to use a slow flow of air because the seal to the skin was rarely completely leak free. In our experience the observations were more easily made on small veins or little telangiectases than on the larger veins.

Tissue pressure. Through the use of a Burch-Winsor manometer (ID)† a determination was made of the pressure at which the entry of saline solution through a No. 27 needle with lateral drilled openings just began. This value was contrasted

*Ciba Pharmaceutical C[illegible] 556 Morris Ave. Summit, N. J.
†[illegible] I131 #6700 Abbott Laboratories Rad[illegible] Pharmaceuticals, Oak Ridge, Tenn.
‡Precision Rate Meter, Curtis Nuclear Corporation, Gardena, Calif.
§Rectiriter, Texas Instrument Corp., Houston, Tex.

*[illegible] #1500, Minnesota Mining C[illegible] 900 Bush, St. Paul, Minn.
†[illegible]manometer W. A. Baum C[illegible] New York.

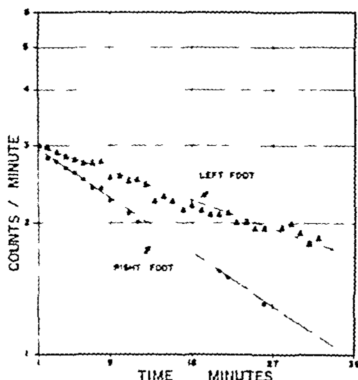


Fig. 1. Shows the drop in I[131] count after injection into the tissues of the foot. *Right foot:* With massage of the calf every 45 seconds. *Left foot:* Control taken 30 minutes later under the same conditions but without massage.

in the two legs after the subject had sat for 2 hours in the erect posture with active massage in the one leg.

Oxygen tension. In 4 subjects an oxygen electrode* was used to measure the oxygen tension of venous blood drawn from a vein in the dorsum of the foot. The tension after a few minutes of massage was contrasted with that during immobility.

Results

I[131] studies. Fig. 1 shows the rate of clearance of I[131] from the feet. The right foot was massaged and the left served as a control. As noted previously, forced and complete immobilization of the foot was not attempted. It was considered that a close approximation to conditions holding in practice would be obtained by merely resting the foot close to a solid object and asking the subject to keep still. For this reason there were a number of small movements which contributed to the observed variations in readings as the count diminished. However, sufficiently reliable curves could be consistently obtained to provide the data for Fig. 2.

The left-hand section of Fig. 2 represents the results obtained in the final experimental form. Six subjects were given injections into the region of the abductor muscle of the fifth toe in order to determine the rate of clearance from muscle in this general area. All subjects showed significantly enhanced clearance of the I[131] after pumping in the calf was initiated after they had sat for 2 hours prior to the test. Since the clearance studies had to be run in sequence, control and massage legs were alternated. Since each clearance curve took 30 minutes to complete, the total seated time was 3 hours, as is indicated in the left-hand section of Fig. 2.

The center section of Fig. 2 presents the time to 50 per cent count in 6 more normal subjects given the I[131] into the first interdigital fold. The area was chosen both because it provided data on clearance

*Beckman Instruments, Inc., Spinco Division, Stanford Industrial Park, Palo Alto, Calif.

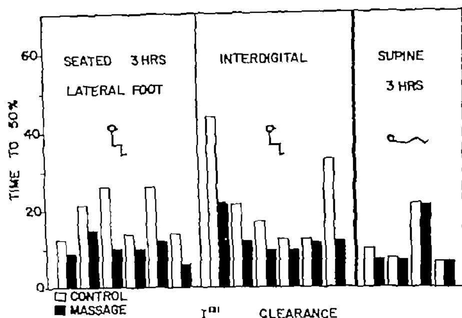


Fig 2 The effects of massage (*crosshatched columns*) are contrasted with a control (*open columns*) without alternation of pressure: In upright seated subjects given I^{131} into abductor of fifth toe (*left-hand panel*) In subjects given I^{131} into the first interdigital fold (*middle panel*) and in subjects given I^{131} into first interdigital fold, in the supine posture with heart slightly below level of foot (*right-hand panel*).

from the skin and because it was typical of tissue that eventually breaks down in arterial insufficiency Again there is a consistent increase in the rate of removal of the injected aqueous solution. Individual differences in the rates of capillary blood flow due to physical training and other factors may have influenced the rate of clearance in the various subjects.[11]

In the right-hand panel of Fig 2 the data for the effects of massage in the recumbent posture are presented Here where there is no rise in venous pressure with dependency and immobility and no consequent venous stasis, the rates of I^{131} clearance remain the same in control and massaged legs.

Fig 3 presents in the left hand panel the contrast between control and massaged clearance after 1½ hours of seated immobility in 8 patients with various grades of arteriosclerotic disease of the extremities. Again there is always an improvement in the I^{131} clearance rate. The right-hand panel shows the prolonged after-effects of massage for 1 hour The patients were seated and one leg was massaged After massage they sat still for a further half hour during which time clearance was measured in the control foot. Following this, an injection was made into the pumped foot and the rate of clearance was determined. The continued improvement in the removal of fluid from the tissues of the leg that had been massaged despite the absence of pumping action in the calf for half an hour prior to and during the I^{131} clearance run indicates that the effects of the massage continue for some time after its cessation.

Fig 4 presents a curve of the changes in venous pressure when massage of the calf of a normal subject is stopped At point *A* marked by an arrow the pump was turned off The rising pressure curve is an expression both of the rate of inflow from the arterial supply and of the integrity of the valves, without which the veins of the foot would immediately fill from above. At point *B* the pump was started The rapid fall in pressure in the foot from over 80 mm Hg to less than 50 mm.Hg is typical of the passive exercise type of curves obtained by this massage technique As the time scale indicates, the rate of massage in this case is very rapid This is because the foot is that of a normal healthy subject, and it had

60
DISEASE SEATED 1½ HRS
DURING PUMPING
AFTER PUMPING
TIME TO 50%
40
20
CONTROL
MASSAGE
I¹³¹ CLEARANCE

Fig. 3. Contrast between the clearance of I¹³¹ after 1½ hours of seated immobility in persons with arteriosclerotic disease of the legs. *Open columns:* No massage. *Crosshatched columns:* Massage. *Left panel:* The I¹³¹ was injected after 1½ hours of seated massage and recording was begun in one leg while leaving the other as control. *Right panel:* After an initial period of 1 hour with massage to one leg and rest for the other, massage was stopped. Both legs remained still for 30 minutes. Finally, I¹³¹ was injected and clearance in the leg which had been massaged previously was compared with that in the control.

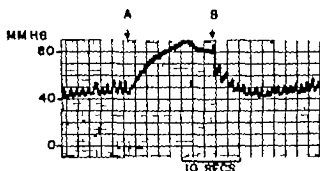


Fig. 4. Changes in venous pressure in the warm foot of a normal subject in the upright seated posture when massage of the calf is stopped (*A*) and then started again (*B*). The gradual rise after *A* represents the filling of the vessels of the leg with blood; the rapid fall after *B*, the quick emptying of the veins with massage. This is carried out at a rapid rate of 1 second on and 1 second off in order to obtain maximum changes despite the rapid flow of blood.

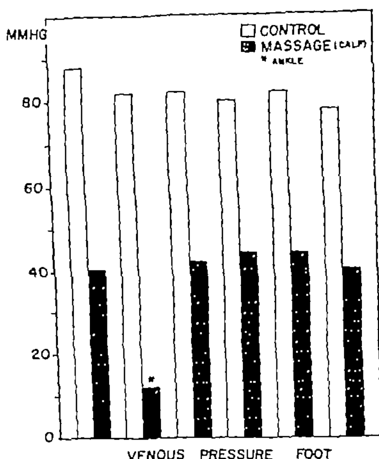


Fig 5 Effect of massage of the calf on venous pressure in the feet of subjects in the erect seated posture. *Open column*: Control. *Cross-hatched column*: Massage. The greater fall in the second case from the left is due to the placement of the massaging band at the level of the ankle.

to obtain maximum venodilation preparatory to venipuncture. As Henry and Gauer[3] have pointed out in their study of the effects of temperature on venous pressure in the foot under such conditions a fast rate (one cycle per 2 seconds) of walking (or massage) is necessary in order to compensate for the rapid inflow of blood and create a significant local drop in venous pressure.

Fig 5 presents in 5 normal cases the extent of reduction in pressure in the veins of the foot of a seated man as the calf is massaged There is a fall of approximately 40 mm Hg in the venous pressure of the foot of the seated subjects confirming the single observation presented in Fig 4

The change in venous pressure during massage in the upright seated posture in the diseased subjects was measured by the capsule. A mean of 5 observations in the same number of subjects yielded an approximate value of 40-mm Hg reduction in pressure during massage.

Because the rate of inflow from the arterial tree is impaired in diseased subjects, the pressure in the veins builds back only very slowly over a period of a minute or more Hence slow massage with cycling rates, such as 15 seconds on and 30 to 45 seconds off is compatible with unimpaired effectiveness of reduction in venous pressure and probably of removal of I[131] as well.

The one case marked ankle in Fig 5 represents an instance in which the massage cuff was placed very low on the leg By so doing venous pressure was correspondingly reduced because the column from the point of massage down to the foot was thereby shortened Th

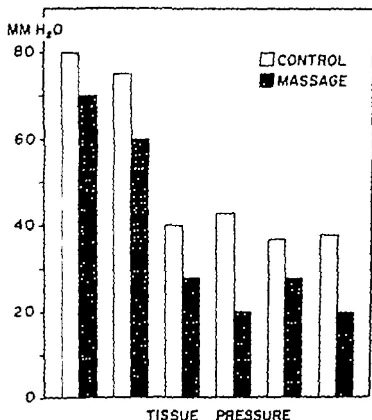


Fig. 6. Effect of massage upon tissue pressure in the foot when the subject is in the upright seated posture. *Open columns:* Controls seated for 2 hours without massage. *Crosshatched columns:* Subject massaged for 2 hours.

shows that the greatest reduction in pressure in the foot would be obtained by eliminating the column above it. This could be done by use of a pressurized combined boot and legging in which the entire lower leg and foot were rhythmically massaged.

Tissue pressure. The data shown in Fig. 6 were collected in 6 normal subjects and show a significant reduction in the tissue fluid pressure as approximately measured by the balancing of an infusion of citrate into the tissues. These observations were made at the end of 2 hours of immobility of the subject in the erect seated posture with and without massage of the calf.

Oxygen tension. Fig. 7 shows the results of four observations made of the oxygen tension in the blood from a major vein in the dorsum of the foot of normal subjects. These samples were taken after a few minutes of massage of the calf. In one case there was a significant increase in oxygen

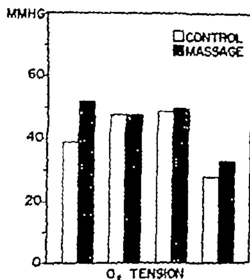


Fig. 7. Changes in oxygen tension of venous blood taken from a vein on the dorsum of the feet of normal subjects in the erect seated posture. *Open columns:* No massage. *Crosshatched columns:* Massage of the calf for 3 minutes. Ordinate: Oxygen tension in millimeters of mercury.

tension and in no case did the condition reverse In contrast with the normal subjects, who showed little cyanosis with dependency the diseased subjects were grossly cyanotic after sitting This condition was visibly improved during massage using a clear plastic boot,* and it has seemed to be a potentially useful clinical measure of optimum rates of pressure and massage. No measurements of venous oxygen content have been made in the patients to determine whether they show changes larger than in the normal subjects. In the discussion the significance of these slight changes in relation to the supply of nutritive blood to the tissues will be presented

Discussion

So far in a limited number of cases the clinical effects of the use of massage in the seated posture have been encouraging and confirm the positive results already obtained by Rodriguez[12] Magnus,[13] Ratschow[14] and Benunson[15] These favorable reports of decreased night pain improved walking distance, and the gradual healing of lesions with persistent treatment require some explanation in terms of physiologic effects. The current paper adds to the evidence already available on the influence of massage upon the total flow of blood through the limb and on venous drainage.

The effects of the upright seated posture upon the arteriovenous pressure differential in the foot are significant. Thus, without massage the venous pressure in the foot is 80 mm.Hg. This pressure counterbalances the gain in pressure of 80 mm.Hg on the arterial side due to the elevation of the heart above the foot. But when the venous pressure is reduced by 30 to 40 mm.Hg, the arteriovenous pressure differential is increased by this amount for as long as massage is maintained The results of Allwood[1] and Loane[3] document the increase in the total flow of blood to be expected as a result of this increase in perfusion pressure. Counterpressure was only applied to the calf in the present studies in order to leave the feet free for the determination of I^{131} clearance and for other observations However if the veins of the foot, as well as those in the calf are compressed then as the histogram marked ankle in Fig 5 indicates, there is an added advantage because the column of blood below the lowest point of venous massage has been shortened as much as possible

Rapaport and associates[6] have pointed out that the supply of nutritive blood to a part furnished with important temperature-regulating arteriovenous anastomoses such as the skin of the foot, must be distinguished from the total flow of blood through the region which may exceed it many fold It was for this reason that the tissue clearance technique was employed in the present studies. It constitutes the most direct measure of the really critical parameter the rate at which metabolites are being washed away by the true capillary circulation[6,7] An overwhelmingly larger total flow of blood through the arteriovenous functional bypasses could well have diluted any change in the oxygen tension of the effluent nutritive blood that may have resulted from the improved arteriovenous pressure differential Thus, despite the insignificant changes observed in venous oxygen tension the clearance studies indicate that even *in the normal* subjects there was a significant improvement in the nutritional circulation

This improvement not only occurred in the diseased tissues during massage but persisted for at least half an hour afterward The mechanism underlying this persistence is not known Perhaps by decreasing the venous pressure and so increasing the true capillary blood flow through the tissues the massage may have increased oxygen tension. In addition one may speculate that the known pumping activity of the lymphatics[17] may have increased as a result of an improved local tissue oxygen tension or other changes Furthermore, the sustained alteration of arterial and venous pressures that accompanies massage leads to a reduced tissue pressure and it takes some time for this tissue pressure to return to the original high values after massage has been discontinued During this period of more nearly normal tissue pressure tissue nutrition may improve

*Air Boot" Pneumatic Pressure Bandage, Jobst Institute.

The more rapid removal of a freely diffusible inert substance and the improved nutritional circulation of which this removal is reliable evidence could well be associated with beneficial effects in terms of the exchange of metabolites at the cellular level. Thus the oxygen content even of normal lymph has been shown by Bergofsky and associates[18] to be extremely low which suggests that the tissues operate at oxygen tensions far lower than those of venous blood. Improved rates of tissue fluid exchange might be associated with slightly raised tissue oxygen tensions. This evidence of an increased nutritional circulation helps to explain the clinical improvement that has been reported in cases of arteriosclerosis obliterans after the use of a massage suit with the patient in the upright seated posture.

Summary

1. The effect of intermittent compressive massage to the lower leg of subjects seated in the upright position was studied in normal persons and in patients with arteriosclerosis obliterans.

2. The measured reduction in venous pressure despite the gravity induced increase in arterial pressure indicated a 40 to 50 per cent improvement in the arteriovenous pressure differential across the tissues of the foot with a corresponding increase in the rate of total blood flow.

3. Measured rates of removal from the tissues of the foot of I[131] injected in aqueous solution showed uniform acceleration both during and after massage.

4. This evidence of improved nutritional circulation in the massaged extremity throws light on the mechanisms underlying the reported clinical improvement that follows such treatment.

We wish to express our appreciation to Randy Leach and to Sally Cody for their unfailing technical support, and to Dudley Kreigbaum for his active collaboration in the early phases of this work. The support and encouragement given by Professor John P. Meehan is gratefully acknowledged. We are also most appreciative of helpful criticism from Dr. Chester Hyman, Dr. Miguel Rodriguez, and Dr. Joseph Benimson.

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The experimental production of coronary sinus rhythm in man

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In 1906 Tawara[1] described specific fibers which enter the proximal portion of the auriculoventricular node from the sinus of the coronary vein. Aschoff[2] later demonstrated that these fibers are derived in common with the sinoauricular node from the primitive sinus tissue and that they unite with the auriculoventricular node to form its auricular portion.

Experimental work showed that warming of the coronary sinus in dogs caused a tachycardia with a normal P R interval.[3] Eyster and Meek,[4] in their experiments in dogs, excised the sinus node and ultimately produced a rhythm whose area of stimulus formation was shown by direct leads to be in the region of the coronary sinus.

Daines and Hecht[5] first produced transient coronary sinus or upper nodal rhythms in man by the intravenous injection of 1 mg of phenylephrine hydrochloride. However until now it has not been feasible to produce this rhythm in man consistently and regularly. The following study employing catheterization of the coronary sinus and pacing with the bipolar electrode catheter was designed for this purpose.

Methods and materials

Catheterization of the coronary sinus was performed in 8 patients undergoing diagnostic right heart catheterization A No 8F Goodale-Lubin thin-wall catheter was used to enter the coronary sinus. Care was exercised not to advance the catheter distally in the coronary sinus toward the left cardiac border Instead the catheter was kept as close to the os of the coronary sinus as possible while still lying in its lumen Position of the catheter was verified by the determination of the oxygen content of samples of blood drawn through the catheter Through this catheter was passed a specially made bipolar pacemaker electrode

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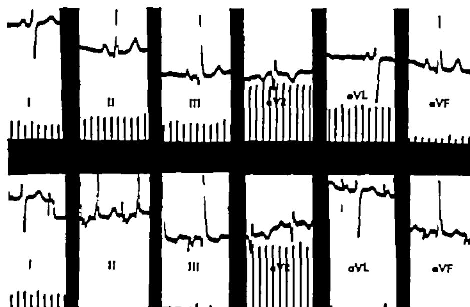


Fig. 1. Standard limb leads in a patient in regular sinus rhythm (*top*) and in the same patient when paced from the coronary sinus (*bottom*).

catheter whose tip extended 1 cm. beyond the tip of the Goodale-Lubin catheter. Pacing was done on a battery-operated cardiac pacer.† Standard 12 lead electrocardiograms were obtained in all patients before and during pacing. In addition, vectorcardiograms employing the cube system of electrode placement were obtained in 4 patients before and during pacing. The horizontal, right sagittal, and frontal plane vectors were recorded on an Electronics for Medicine photographic recorder. All patients were in regular sinus rhythm at the time the study was made, except for one patient, who satisfied the criteria for coronary sinus rhythm.

Results

Pacing. Pacing was easily accomplished in all patients and could be maintained without difficulty. In each case the rhythm produced was regular, with P waves that preceded the QRS. The contour of these newly formed P waves was altered: the P waves were negative in Standard Leads II, III, aVF, upright in Lead aVR, and flat or upright in Lead I (Fig. 1). The QRS was unaltered in contour or duration. Cessation of the pacing stimulus resulted in immediate return of the patient's previous rhythm.

P-R intervals (Table I). The P-R interval varied between 0.13 and 0.24 second during pacing. The one prolonged value, i.e., 0.24 second, was in a patient who had first degree heart block and a control P-R interval of 0.30 second. In 6 of 7 patients this value ranged from 0.01 to 0.06 second less during pacing than during the control rhythm. This shortening cannot be attributed entirely to a faster rate, since shortening of the P-R interval also occurred in 2 patients in whom the control and paced rates were nearly the same. Only one patient had a greater P-R interval when paced than when in normal sinus rhythm. Patient C. C. had a P-R interval of 0.20 second during spontaneously occurring coronary sinus rhythm; when this same rhythm was produced by pacing, the P-R interval was 0.19 second (Fig. 2).

Vectorcardiograms. The mean P wave vector during pacing was directed superiorly, anteriorly, and slightly to the right. Only the patient with known left atrial enlargement had a posteriorly directed loop (Fig. 3). The mean vector of the patient with spontaneously occurring coronary sinus rhythm was directed superiorly, slightly posteriorly, and to the left; when the patient

*United States Catheter and Instrument Corporation, Glens Falls, N. Y.
†Westinghouse Electric Corporation, Baltimore, Md.

Table 1

Patient	*Control*			*Paced*		
	P R (sec.)	*QRS (sec.)*	*Rate per minute*	*P R (sec.)*	*QRS (sec.)*	*Rate per minute*
L.A.	0 19	0 10	68	0 19	0 10	100
C.B	0 15	0 07	72	0 13	0 07	102
D H	0 18	0 08	80	0 15	0 08	120
B.F	0 14	0 07	66	0 13	0 07	106
G.J	0 20	0 08	75	0 18	0 08	68
C.C.	0 20	0 08	90	0 19	0 08	104
B.R.	0 30	0 09	68	0 24	0 09	76
L.J	0 16	0 08	60	0 18	0 08	86

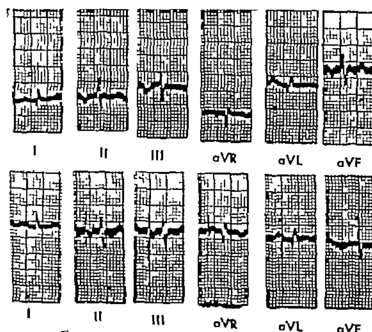


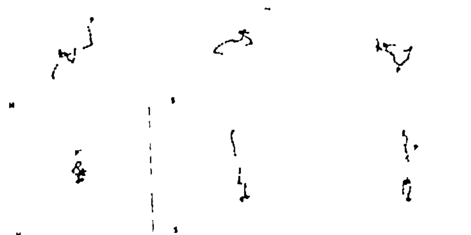
Fig 2 Standard limb leads in a patient in spontaneous coronary sinus rhythm (*top*), and in the same patient paced from the coronary sinus (*bottom*). Note the similar P-wave contour in both electrocardiograms when paced, the P R interval is 0 01 second less than in the control rhythm.

was paced, the vector was still directed superiorly but had moved anteriorly and slightly to the right (Fig 4) The mean frontal plane axis was −105 degrees and varied between −95 and −120 degrees.

Discussion

The auriculoventricular node lies at the *posterior and right* border of the interatrial septum close to the origin of the coronary sinus.[8] When the pacemaker is transferred to the A V node, the seat of impulse formation is usually transferred to the coronary or proximal portion of the node. Under such circumstances, atrial excitation is retrograde and the P waves are inverted in Leads II III and aVF and upright in Lead aVR of the standard electrocardiogram.[7]

For descriptive purposes, three types of A V nodal rhythm are generally described



I 3 Horizontal sagittal nd front l l w h left atrial argement in regular inu rhythm (p ...nary sinu bottom

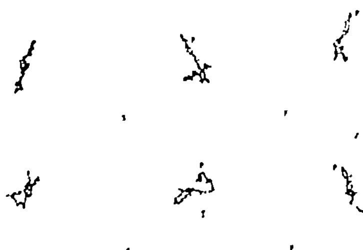


Fig 4 Horizontal sagittal and frontal plane l-w v ect rs n a patient w th spontaneous coronary nus rhythm (top) and when paced from the coronary sinus (bottom) Note the similarity of the mean frontal plane vectors.

i e. upper middle or lower nodal depending upon whether the formation of impulses occurs in the proximal middle or lower most portion of the A V node In upper A V nodal beats the impulse has to travel a short distance in its retrograde spread to the atria whereas it must traverse the entire length of the node to reach the ventricles thus resulting in a retrograde I wave that precedes the QRS Because antegrade and retrograde conduction require the same amount of time in mid-nodal rhythm the P wave is buried in the QRS In lower A V nodal rhythm excitation of tl ventric occurs sooner than that a ly I wave follows the QI S c

Although this cla fica ment it must be remembe ed th ntegrade retrograde condu tion are urring taneously and the I R int al ment resents the algebr ic sum these co tion times thu any of ne P-QRS tion ships may prevail ir spective part of the node from w ich the arises If there is impairme nt of condu in any direction The above-mentione

sification is valid only if the rates of conduction in both directions are equal.[7]

Coronary sinus rhythm is considered by some to be synonymous with upper nodal rhythm. Still others reserve the name "coronary sinus rhythm" for that type of A-V nodal rhythm in which the characteristic P waves precede the QRS, and in which the P-R interval is 0.12 second or longer. Those rhythms with shorter P-R intervals are considered to be representative of upper nodal rhythm. This distinction is based on the belief that in coronary sinus rhythm the impulse arises in that part of the A-V node closest to the os of the coronary sinus vein and that such impulses enter the atria directly, whereas the antegrade conduction to the ventricles must traverse the entire length of the node; thus in coronary sinus rhythm the P wave appears earlier and the QRS later than in upper A-V nodal rhythm per se. This distinction is certainly not absolute and is only one of degree; certainly it bears no clinical significance.

That the rhythm produced in the present study fulfills the criteria for coronary sinus rhythm is apparent. The P waves preceded a normal-appearing QRS and were inverted in Standard Leads II, III, and aVF in all cases. The mean P wave vector in the frontal plane was superiorly directed and slightly to the right, reflecting the retrograde conduction of the impulse through the atria, and was in contrast to the inferiorly and usually leftward directed P wave seen in normal sinus rhythm.[6] That the P-R interval in no case was less than 0.12 second precludes this being called upper nodal rhythm on the basis of the aforementioned criteria.

The name "coronary nodal rhythm" has been used when, with the P-R interval between 0.02 and 0.10 second, the P waves in Standard Leads I and II are upright. The impulse in such cases supposedly arises in the region closest to the tail of the sinus node and spreads in a normal fashion, producing a P wave pattern not unlike that seen in regular sinus rhythm. Such terminology is confusing. Certainly this study refutes this pattern as arising from the area of the coronary sinus. Coronary nodal rhythm more than likely represents a variant of normal sinus rhythm, such as that arising along an anomalous conduction pathway that bypasses the auriculoventricular node.

Subject to considerable doubt is the statement that if in coronary sinus or upper nodal rhythm the P-R interval exceeds 0.12 second, some degree of A-V block must be present.[9] This was not apparent in the large series of Scherf and Harris,[10] who compared the P-R intervals in both rhythms. Moreover, in the present study the P-R interval during pacing was always in excess of 0.12 second, and there was no evidence of A-V block during regular sinus rhythm. One patient with A-V block (P-R of 0.30 second) had a P-R of 0.24 second in coronary sinus rhythm. However, it should be noted that the P-R interval in coronary sinus rhythm, although not abbreviated, is in most cases less than the P-R interval in normal sinus rhythm in the same patient.

Summary

Coronary sinus rhythm was produced experimentally in 8 patients, utilizing the bipolar pacing catheter in the os of the coronary sinus.

The distinction between coronary sinus rhythm and upper nodal rhythm is again seen to be an arbitrary one. The value of the P-R interval in coronary sinus rhythm and its relation to A-V block is discussed.

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Contracting chicken embryo heart cells in tissue culture

Effect of viruses and other agents

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Cultivation of contracting myocardial cells both singly and in the sheet from suckling rats has been described by Harary and Farley.[1-4] They observed that (1) rat heart cells continued to contract for 40 days when grown in vitro, (2) single isolated cells contracted at an independent rate in the same culture but the rate became synchronous upon physical contact of the cells with one another, indicating communication of the rate of contraction by protoplasmic contact, (3) the rate of contraction increased as the temperature was raised from 23 to 34 C, (4) the rate of contraction remained constant from pH 7.0 to 8.5, (5) acetylcholine and dinitrophenol inhibited contraction, whereas ouabain and adenosine triphosphate, respectively, reversed the inhibitions, and (6) a process of cellular differentiation was apparently accompanied by loss of striations and cessation of contraction. Because relatively little has been done with the rat or its tissues in viral research, it seemed to be preferable to use a well-known host, the chicken embryo, for investigation of viral effects on an infrequently observed tissue, such as the heart.

Recent interest in the effects of viruses on the myocardium has stimulated a search for experimental models. Tissue culture systems have been used extensively in the study of the effects of viruses on cells; therefore, it seemed logical to utilize a similar system to study the myocardium. Embryonated eggs, or cultures prepared from the embryo or its components, have provided useful systems for studies on cells and their metabolism, as well as the effect of viruses. Accordingly, techniques were devised for the preparation of tissue cultures containing contracting heart cells from the embryonated egg. Observations were then made on the toxic effect and propagability of viruses in these cultures. In most instances, background information on the effect of these viruses on other hosts and types of tissue cultures was already available. In this paper it will be shown that toxic effects were demonstrable with certain viruses, but evidence of multiplication was not obtained. Certain other characteristics of these heart cell cultures were also investigated, such as the effect of drugs, amino acids, calcium chloride, and electricle stimulation on contraction.

Methods

Preparation of cell cultures. Contracting chicken embryo heart cultures (CEHC)

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were prepared from the hearts of 11 to 19-day-old white leghorn chicken embryos 30 or more were used for each experiment. Most cultures were prepared with 13- to 14-day-old embryos. The hearts were removed aseptically placed in a Petri dish containing Hanks balanced salt solution[6] trimmed free of large blood vessels, pooled minced with scissors, and washed three times with Hanks solution the cells were then dispersed at room temperature with 0.25 per cent trypsin (Difco 1:250) in phosphate buffered saline (PBS) diluted to 0.1 per cent with Hanks solution (final pH = 7.5) in a flask with a magnetic stirrer Trypsin in concentrations of 0 075 or 0.2 per cent resulted in less satisfactory dispersion and/or growth and fewer beating areas. Versene (disodium dihydrogen versenate) 0 02 per cent in PBS and 0 01 per cent collagenase* were unsatisfactory as cellular dispersing agents. The first 10-minute extraction was discarded Six to eight additional 15-minute extractions were usually sufficient for complete dispersion. Each extraction was packed at 1 000 r.p.m. for 10 minutes, the trypsin was decanted and the cells were pooled into 1 to 4 ml. of Hanks solution. The final packed cell volume (usually 0.2 to 0.3 ml. per 10 hearts) was planted at a dilution of 1 100 (1 to 1.5 million cells per milliliter) in Eagle's minimum essential medium[7] in Earle's balanced salt solution[8] with 200 units per milliliter of penicillin, 100 μg per milliliter of streptomycin and 5 per cent unheated calf serum Chicken embryo heart cells grew and contracted when 1 2 3 4, or 10 per cent calf serum was used however 5 per cent appeared to produce the greatest yield of healthy contracting cells. The use of chicken serum, horse serum (5 10, or 15 per cent) or both, and nystatin (25 units per milliliter) resulted in early cellular degeneration. In some experiments, various components of Eagle's medium were deleted or substitutions were made.

Cells derived from the lungs, allantoic membrane and legs of chicken embryos were prepared and cultured as described Contracting cells, originally described by Lewis[9] and recently studied by Konigsberg[10] were grown from the leg. Adult monkey and rabbit hearts were treated as described except that 0.2 per cent trypsin was used to disperse the rabbit heart, and the cells were planted at dilutions of 1 75 and 1.50 respectively Only cells resembling fibroblasts grew and no contracting was observed.

The cells were propagated at 35°C in stationary culture tubes, Petri dishes prescription bottles and on coverslips Chicken embryo heart cells could be satisfactorily propagated at 30 and 37°C., as well as after storage for 24 hours in growth medium at 4°C When the cells were cultured at room temperature an initial growth phase was followed by early degeneration and no contracting was observed Chicken embryo heart cells grown on coverslips were studied using phase electron fluorescent, and ordinary light microscopy the latter with a variety of stains.

After 24 to 48 hours the growth medium was discarded and the cells were washed twice with Hanks solution Maintenance media consisted of the growth medium without calf serum. The pH of all media was lowered by saturating with carbon dioxide so that it was 7 0 to 7 2 at 35°C.

Indirect fluorescent stains Chicken embryo heart cells were grown on coverslips and inoculated with viruses or control material. After 6 to 24 hours the coverslips were removed washed three times in PBS (pH 7 2) dried 1½ hours at 37°C. placed in acetone at 4°C for 10 minutes and dried 30 minutes at 37°C Coverslips were utilized immediately or stored at 20°C Acute and convalescent rabbit antisera prepared as previously described[11] were applied for 20 minutes at 37°C in a humid environment. After the coverslips had been washed in three changes of PBS for 10 minutes, sheep antirabbit globulin conjugated with fluorescein diluted 1-4 in distilled water was added The conjugated globulin had been absorbed twice with 14-day-old chicken embryo heart powder 100 mg per milliliter for 1 hour at 4°C before being left on the coverslip for 30 minutes The coverslips were then washed five times in PBS and left in fresh PBS for 10 minutes. They were mounted in a 10 per cent solution of glycerol in saline sealed with clear fingernail polish and ex

*Sylvana Chemical Co Orange N J

amined through a Leitz Ortholux ultraviolet microscope. Appropriate controls were obtained with each group of slides. No green CEHC or antiserum autofluorescence was observed. This fluorescent technique is a modification of one used by Weller and Coons for coverslip preparations.[12]

Viruses. The viruses used in the experiments and their source (chicken embryo or cell culture) are listed in Table I. Most of the viruses used were isolated, maintained, and stored (−70°C.) in this laboratory in connection with other studies.[13]

Hemagglutination (Ha). Serial twofold dilutions of virus or tissue culture fluid were made in PBS (pH 7.2) for determination of hemagglutination titers. An equal volume of 0.5 per cent human group O red blood cells was added and allowed to sediment at 4°C. (room temperature for parainfluenza viruses) for 2 hours.[13] Chicken

Table I. Effect of viruses on chicken embryo heart cultures

Virus	Source*	Cytopathic effect	Virus titers log					
			Ha†			ID50†		
			Days			Days		
			0	3	5-6	0	3	5-6
Adenovirus								
Type 3	MK	0				1.0	0	0
Type 4	MK	0				0.5	0	0
Type 7	MK	0				0.5	0	0
Coxsackie								
A9	KB	0				3.0	1.0	0.5
A21	KB	0				4.5	1.5	0.5
B2	KB	0				6.5		
B3	KB	0				7.0	6.5	3.5
Influenza								
A/PR-8/34	CE	+	3.9	2.4	2.4	8.0	6.5	2.5
A/Swine	CE	0	3.9	1.8	<0.6	5.5	0	0
A2/N.Y./1/57	CE	+	3.6	1.5		8.0	0	
	MK	0	2.1	0.9	<0.6	6.0		
B/K302/59	CE	+	3.9	2.1		7.5	0	
	MK	0	2.1	1.5	<0.6	5.0		
B/Lee	CE	0	3.5	1.5	0.9	6.5	0.5	0
C/N.Y./1/60	CE	0	6.3	3.3	3.0	6.0		1.0
	MK	0	4.5	2.4	2.1	5.0		
Murivirus								
1/GL2060/54	KB	0				3.5	0.3	0
Parainfluenza								
1 (Ha-2)	MK	0	1.8	<0.6	<0.6			
1 (Sendai)	CE	+	4.5	3.6	3.3	8.0	5.5	3.5
2 (CA)	HeLa	0	1.2	<0.6	<0.6	2.5	0	0
3 (Ha-1)	MK	0	2.1	<0.6	<0.6			
Respiratory syncytial	KB	0				2.0	0	0

*MK, Monkey kidney tissue culture. KB, Nasopharyngeal epidermoid carcinoma cell culture.[14] CE, Chicken embryo. HeLa, Cervical epidermoid carcinoma cell culture.

†Logarithms of the reciprocal hemagglutination (Ha) and infectivity (ID_{50}) titers are shown.

red blood cells (0.5 per cent) were used for influenza C.[16] Titers were read as the final dilution showing visible agglutination by the pattern method.

Infectivity for chicken embryos (EID_{50}). Tenfold dilutions of virus or CEHC fluid in Hanks solution were inoculated allantoically (0.1 ml.) into groups of two 10-day-old embryonated eggs. After 3 days of incubation at 35°C. the eggs were chilled and the allantoic fluid was harvested. Infection was determined by the presence of virus hemagglutinins, and the ID_{50} was calculated by the usual method.[17]

Infectivity for tissue culture ($TCID_{50}$). Groups of two KB cultures were inoculated with 0.1 ml. aliquots of tenfold dilution of virus. The cultures were examined microscopically (× 100) for cytopathic effect for 3 to 4 days. Infectivity titer was determined on the basis of the presence of specific cytopathology on the last day of observation and calculated as before.[7] Monkey kidney cells were propagated as described previously[8] and infectivity titers were determined in the same way as in KB cell cultures.

Results

Histologic appearance of chicken embryo heart cells. Sixteen to 24 hours after chicken embryo heart cells were planted, scattered areas began to contract at rates of 20 to 120 per minute. These areas were designated "microexplants" to distinguish them from single cells which were also present but usually did not contract. Decreasing the concentration of chicken embryo heart cells per milliliter of growth medium did not increase the number of isolated contracting cells. After 36 to 48 hours the cell sheet became confluent and many of the cells between the "microexplants" assumed a three-dimensional appearance. Chicken embryonic fibroblasts appeared as flat cells in culture.

During the third to sixth days of incubation contracting areas other than the "microexplants" were seen. These new contracting areas consisted of one or more cells that usually assumed a three-dimensional appearance in the medium (Fig. 1A). The presence of contraction and the apparent increased substance of these cells support the contention that they represented muscle cells.

Cross striations. Cells grown on cover slips were studied in an attempt to define the morphology of the contracting and noncontracting cells. Examination of fresh nonfixed specimens with phase microscopy failed to reveal cross-striations, even in cells that were contracting during observation. Coverslip specimens were fixed in methacrylate and sectioned for electron microscopy. Limited studies have revealed cells at any early stage of development that could not be classified as to type (fibroblast or heart myoblast).

Use of phosphotungstic acid hematoxylin, Gomori's one-step trichrome and iron hematoxylin stains established the presence of cells with cross-striations typical of muscle cells and many of the cells were multinucleated as well. Immature cells without striations were also seen (Fig. 2).

Contraction. The number of contracting or beating areas varied considerably in different cultures and within the same culture from day to day. The rate and rhythmicity varied in a similar fashion. As the temperature decreased from 35°C. the rate and total number of contracting areas decreased. Intermittent beating was common, especially at room temperature. Cessation of contraction occurred after 10 minutes to 3 hours at room temperature. Contraction was observed when the pH of the media was 6.9 and 7.8. The usual pH of the media (7.0 to 7.4) appeared to be the optimum for contraction.

When the maintenance medium was replaced every 3 to 4 days, the cell sheet could be preserved for several weeks; otherwise, degeneration began after 1 or 2 weeks. Two types of degeneration occurred. One was characterized by curling of the sheet off the glass, with granularity of the cytoplasm and some cell destruction. The other type manifested as cell-free spaces developing in the sheet (Fig. 1B). Frequently parts of the sheet between the spaces appeared to be compressed together resembling a fiber. These "fibers" were often observed to contract vigorously. Usually larger areas were contracting together as if the compactness of the original solid sheet had inhibited contraction by diffusing the impulses in all direct-

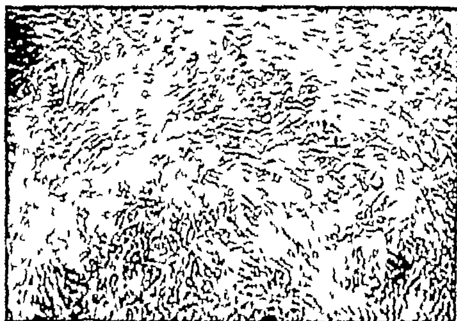


Fig. *1.* Chicken embryo cells cultured in 16-by 125 mm. tubes (×100 magnification). *A.* CEHC after 6 days of incubation. The "ridged" appearance is readily apparent.

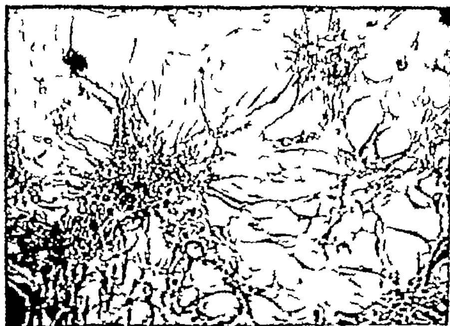


Fig. *1,B.* CEHC after 30 days of incubation. Note the holes in the sheet and the "fibers" formed between them. Beating was active in this network of cells.



Fig. *1 C.* Third passage of CEHC after 8 days of incubation, illustrating fibroblastic-appearing cells with a "microexplant" that was beating



Fig. *1 D.* CEHC 3 days after inoculation with influenza B/K-302/39 virus. The rounded cells and cellular debris also occurred after inoculation with influenza A/PR-8/34 and A2/NO 1/57 and parainfluenza 1 Sendai/52 viruses.

Table II. Effect on chicken embryo heart culture cells of omitting glutamine, other essential amino acids, or calcium chloride from maintenance medium

Eagle's medium			Number of experiments	Total days of observation	Days beating observed		Increased cell degeneration observed with depleted medium
Glutamine*	Amino acids*	Calcium chloride*			Depleted medium	Control medium†	
100	0	100	9	60	39	18	+
0	100	100	5	27	19	10	+
0	0	100	3	11	4	6	+
100	25	100	3	29	18	4	+
100	50	100	4	33	20	5	+
100	5	100	3	29	20	7	±
100	100	0	3	29	0	18	+
100	100	25	2	11	4	8	0

*Expressed as the per cent of the usual amount.
†Complete Eagle's maintenance medium.

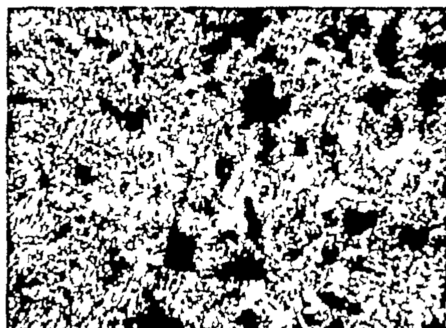


Fig. 2. Stained coverslip cultures of chicken embryo heart cells (CEHC). A, CEHC after 48 hours of incubation. Note the heavily stained microexplants. Phosphotungstic acid hematoxylin (PTAH) stain (×35).

rather than creating a functioning connecting network of fibers.

Stimulation of contraction

DRUGS. Chicken embryo heart cells could be stimulated to contract and the rate of contraction in other cells could be increased by the addition of pilocarpine, strophanthin K, or carbamylcholine (0.1 mg. in 0.1 ml. distilled water per 1.0 ml. of media). The CEHC were grown in Petri dishes (5.0 ml. of media) and kept at room temperature during these observations. The pH of the media was kept between 7.0 and 7.4 throughout these experiments by using a balanced salt solution composed of 75 per cent Hanks' and 25 per cent Earle's solutions. The drug stimulatory effect usually persisted for 1 to 5 minutes.

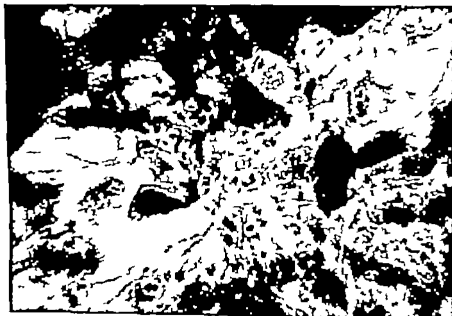


Fig. 2.B CEHC after 48 hours of incubation stained with Gomori's one-step trichrome. Cross-striations are easily seen (X970).



Fig. 2 C, CEHC after 96 hours of incubation stained with iron hematoxylin. Note the multinucleated cells typical of muscle (X430).

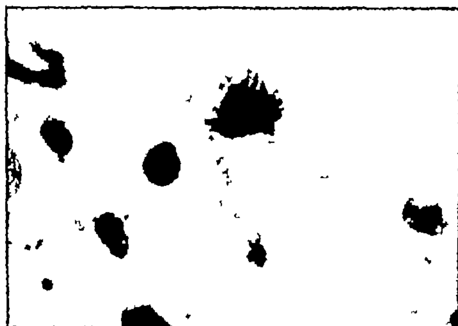


Fig. 2.D. CEHC 24 hours after inoculation with parainfluenza 1/Sendai virus. Note cytoplasmic shrinking and clubbing. Pyknotic nuclear fragments are also seen. Giemsa stain (×970).

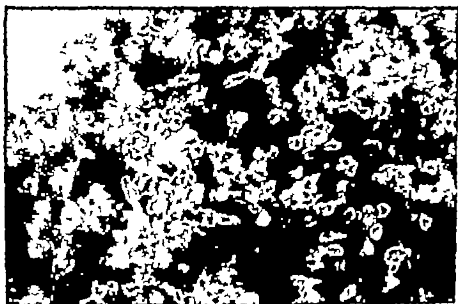


Fig. 2.E. CEHC 24 hours after inoculation with parainfluenza 1/Sendai virus. Indirect fluorescent antibody technique. Note prominence of fluorescein staining in the perinuclear cytoplasm of the rounded cells (×430).

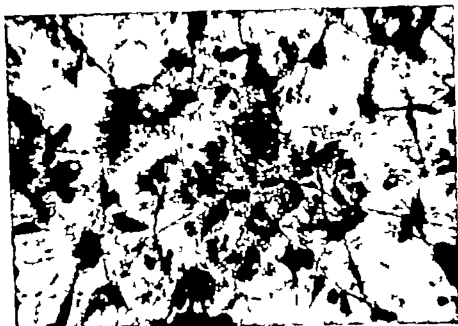


Fig. 2 F CEHC 24 hours after inoculation with influenza A2 virus. Note dense nuclear fragments and debris. Giemsa stain (X430).

Stimulation of contraction after addition of the foregoing drugs may represent a specific effect or only a nonspecific irritation. In comparison however quinidine atrophine epinephrine and norepinephrine (0 001 to 0 1 mg in 0 1 distilled water per milliliter of media) did not affect beating.

ELECTRICAL. Chicken embryo heart cells were grown in Petri dishes as previously described. Two electrodes of an electrical stimulator* were placed in the chicken embryo heart cell culture fluid on opposite sides of the 43X objective (also in the fluid) which was focused on one or more contracting cells. In preliminary experiments definite stimulation of contraction was noted after 0 2 0 3 1 0 or 2.0 volts of stimulation had been administered one or two times per second as a 1-second shock. The rate of contraction increased as much as 50 per cent. There was a maximum rate obtainable which varied from cell to cell.

Effect of omission of components of maintenance medium. Components of Eagle's medium were omitted in order to observe effects of depletion. In some experiments, all amino acids were withheld and in others glutamine was the *only* amino acid included or excluded (Table II). The cells were washed twice with Hanks solution before the addition of depleted medium and the fluid was changed every 3 to 5 days in order to remove residual quantities of these substances and to further deplete the cells.

The number of contracting cells, as well as the rate of contraction increased about 48 hours after media made with glutamine as the *only* included *or* excluded amino acid was added. Both types of cell degeneration discussed previously appeared earlier (1 to 9 days) if the depleted maintenance media were used. If the media contained a normal amount of glutamine (0 292 mg per milliliter) and 75 per cent of the normal amount of essential amino acid concentrate stimulation of contraction occurred without significant early cellular degeneration. If both glutamine and the amino acid concentrate were absent from the media, the amount of beating was less than in the control cultures.

Omission of calcium chloride (0 2 mg per milliliter) from the maintenance medium resulted in cessation of all contracting within 24 hours. Addition of 0.05 mg of calcium chloride per milliliter allowed

*Model 340, Harvard Apparatus Co., Dover, Mass.

some contracting to persist (Table II). Depletion of the vitamins and/or glucose from Eagle's medium did not affect contraction or result in early degeneration. Substitution of lactose for glucose resulted in cellular degeneration within 3 days.

Chicken embryo heart cell subcultures. In order to determine whether chicken embryo heart cells could be subcultured with continuation of contraction, they were grown in a 32-ounce prescription bottle, treated with 0.25 per cent trypsin for 10 minutes to separate the cells, and planted in twice the original volume of growth medium (in two 32-ounce prescription bottles). This procedure could be repeated for five generations; however, the chicken embryo heart cells rapidly differentiated into or were replaced by fibroblastic cells (Fig. 1C). Rare contracting cells were present in second, third, and fourth generation cultures, but none in later ones, even though the cells were concentrated in 50 per cent of the original volume rather than planted in twice the volume as described.

Virus effect. When the chicken embryo heart cells had formed a sheet, they were washed free of growth medium, maintenance medium was added, and viruses were inoculated (Table I). Growth of several viruses could *not* be demonstrated by an increase in hemagglutination or infectivity titers in chicken embryo heart cell culture fluid after 3 and 5 to 6 days of incubation. Four (influenza A PR 8 34, A2 N O 1 57 and B K 302 59, and parainfluenza 1 Sendai/52) of the seven egg-adapted viruses produced a cytopathic effect. However, even three passages of undiluted and diluted virus-inoculated tissue culture fluid (in the same and other chicken embryo heart cell culture experiments) failed to adapt the four viruses for growth in the chicken embryo heart cell. Cytopathic effect was not produced with passaged fluid.

The cytopathic effects produced in chicken embryo heart cells by the four viruses were similar and easily recognizable 12 to 24 hours after inoculation. The effect consisted of cytoplasmic shrinking and clubbing of the cell membrane, which resulted in rounded cells easily demonstrable with the indirect fluorescent antibody technique, as well as with other stains. This process began at the edge of the cell sheet (Fig. 1D). It was most pronounced after inoculation with Sendai virus (Figs. 2D and 2E). Dense nuclear fragments were rapidly formed, with pyknotic nuclear debris as a final result (Fig. 2F). Despite extensive damage to 75 per cent of the cells, others appeared to be normal and some of these were observed to contract at normal rates. Coverslip preparations of chicken embryo heart cells demonstrated an earlier and more pronounced viral cytopathic effect than did those grown on the sides of a test tube, apparently because of environmental or physical differences or both.

Only viruses with relatively high titers produced cytopathic effects in chicken embryo heart cells (Table III). Maximum cytopathic effect was produced in 24 hours for all dilutions of influenza A that resulted in the cytopathology; however, all the chicken embryo heart cells were not destroyed even when undiluted infected fluid with $10^{8}EID_{50}$ was inoculated. In contrast, all the chicken embryo heart cells were destroyed by the third day of incubation after inoculation with the other three viruses (Table III). After 24 hours the cellular debris might have acted as an additive toxic factor. The day of onset of maximum cytopathic effect was delayed when lesser amounts of influenza A2 and B viruses were inoculated, but this did not occur with influenza A (PR8) and Sendai viruses. The Sendai virus apperared to be the most toxic for chicken embryo heart cells.

In order to determine whether the cytopathic effect produced in chicken embryo heart cells by the four egg-adapted viruses was specific for chicken embryo heart cells, these viruses were inoculated into cultures of other types of cells (Table IV). The cytopathic effect produced in chicken embryo lung and leg cells was similar to that produced in chicken embryo heart cells. Monkey kidney-cell-adapted influenza A2 and B viruses did not produce a cytopathic effect in chicken embryo heart cells. The egg-adapted influenza B virus also produced a cytopathic effect in KB, human embryonic kidney, and adult monkey and rabbit heart fibroblast cells.

*Table III. Cytopathic effect (CPE) produced by egg-adapted influenza A, A2 and B and parainfluenza 1 (Sendai) viruses in chicken embryo heart cell cultures**

Virus	EID_{50}†	Hemagglutination†	Reciprocal of final dilution‡	Per cent of cells showing CPE	Day of onset of maximum CPE
Influenza A/PR-8/34	8 0	3 9			
		3 6–3 9	10–20	5	1
		3 0–3 3	40–80	50	1
		2 4 2	160–320	25	1
		2 1	640	0	
Influenza A2/N O 1/57	8 3	3 6			
		3 6	10	100	3
		–3 3	20–80	100	6
		4	160	5	2
		2 1	320	5	4
		1 8	640	50	6
		1 5	1 280	0	
Influenza B/K302 59	5	3 9			
		3 3–3 9	10–40	100	3
		3 0	80	100	4
		2 7	160	100	8
		2 4	320	5	7
		2 1	640	50	7
		1 8	1 280	0	
Parainfluenza 1/Sendai/51	8 5	4 5			
		3 3–4 5	10–160	100	3
		2 4–3 0	320–1 280	100	4
		2 1	2 560	50	2
		1 8	5 120	0	

*Infected allantoic fluid in 0 1-ml. amounts was inoculated into chicken embryo heart cell (CEHC) cultures containing 1 0 ml. of maintenance medium

†Logarithms of the reciprocal hemagglutination (Ha) and infectivity (EID_{50}) titers are shown.

‡Final dilution of virus in CEHC culture maintenance medium.

Monkey-kidney-cell-adapted influenza A2 and B viruses did not produce any cytopathic effect in monkey heart fibroblast cells

In the absence of evidence of virus growth the cytopathic effect produced by the four viruses in chicken embryo heart cells appeared to be due to toxicity without viral multiplication Experiments were performed in order to study the toxic property Heating the viruses at 56°C for 30 minutes resulted in the loss of infectivity for chicken embryos and cytopathic effect in CEHC even though hemagglutinating activity was retained (Table V)

The cytopathic effect produced in CEHC by influenza A2 and B and Sendai viruses could be completely prevented by specific rabbit antisera.[11] Only low dilutions of antiserum were effective because high titered virus was required to produce a cytopathic effect in control chicken embryo heart cells. (See Tables III and V)

Discussion

Chicken embryo heart explants usually in plasma clots have been grown in vitro observed to contract and studied since Carrel s early work. Although cells thought to be cardiac muscle cells have been observed to extrude from these explants for short distances most of the cells away

*Table IV. Cytopathic effect produced by influenza A, A2 and B and parainfluenza 1 (Sendai) in chicken embryo heart cells compared with other types of cells**

Virus	Source	EID50†	TCID50†	Ha†	Chicken embryo heart	Chicken embryo lung	Chicken embryo leg	Human embryonic kidney	KB	Monkey heart fibroblasts	Rabbit heart fibroblasts
Influenza A/PR-8/34	CE	8.0		3.9	+		+				
Influenza A2/N.O.1/57	CE	8.0		3.6	+	+	+	0	0		+
	MK		6.0	2.1	0					0	
Influenza B/K302/59	CE	7.5		3.9	+	+	+	+	+	+	+
	MK		5.0	2.1	0					0	
Parainfluenza 1/Sendai/52	CE	8.5		4.5	+		+				

*Infected allantoic fluid in 0.1 ml. amounts was inoculated into cell cultures containing 1 ml. of maintenance medium.
†Logarithms of the reciprocal infectivity (EID_{50}) and ($TCID_{50}$) and hemagglutination (Ha) titers.

Table V. Inhibition of viral cytopathic effect (CPE) in chicken embryo heart cell cultures by specific antiserum or heat inactivation† of the virus*

Virus	Condition	Ha‡	EID50‡	CPE
Influenza A/PR-8/34	Unheated	3.3	8.0	+
	Heated	3.0	0	0
Influenza A2/N.O.1/57	Unheated	3.6	8.3	+
	Heated	3.6	0	0
	Preimmune serum 1:2	3.3		+
	Immune serum 1:2			0
	Immune serum 1:4	<0.6		0
	Immune serum 1:8	<0.6		+
Influenza B/K302/59	Unheated	3.9	7.5	+
	Heated	3.9	0	0
	Preimmune serum 1:2	<0.6		+
	Immune serum 1:2			0
	Immune serum 1:4	<0.6	0.5	0
	Immune serum 1:8	<0.6		+
Parainfluenza 1/Sendai/52	Unheated	4.5	8	+
	Heated	<0.6	0	0
	Preimmune serum 1:2	2.1		+
	Immune serum 1:2	<0.6		0
	Immune serum 1:4	<0.6	0	0

*Antiserum was prepared in rabbits.
†56°C. for 30 minutes.
‡Logarithms of the reciprocal hemagglutination (Ha) and infectivity (EID_{50}) titers are shown.

from the explants resembled fibroblasts. Because of the immaturity of the cells, if contraction had not occurred their muscle nature could not have been ascertained.[19] Cavanaugh[18] has grown chicken embryo heart cells using the plasma clot technique. Improved techniques for characterization of muscle cells are being reported with increasing frequency. These include cold 50 per cent glycerol extraction of cells grown in vitro to make cross-striations more apparent[19] and use of fluorescent-labeled antimyosin.[20]

By means of a technique similar to that described by Harary and Farley[1-4] for cultivation of heart muscle cells from suckling rats, contracting chicken embryo heart cells were grown by ordinary tissue culture techniques and without the necessity of a plasma clot. Fertile eggs are readily available in large numbers, relatively inexpensive, simple to incubate, and easy to handle. Large numbers of tubes or other containers of chicken embryo heart cultures (CEHC) were easily cultured at one time. The effect of various substances, such as drugs and toxins, applied directly to contracting heart cells can be evaluated. The stimulating effect on contraction of pilocarpine strophanthin K, and carbamylcholine was recorded in the present report. The toxic properties of compounds may be more apparent when applied to a single sheet of cells than to an explant or whole organ in an intact animal. Use of CEHC as an adjunct to pharmacologic screening of drugs possibly affecting the heart should be considered.

Attempts to cultivate contracting heart cells from adult mouse, rabbit, and monkey hearts and fetal human hearts by the technique described have uniformly produced only the noncontracting fibroblastic type of cells. Others[21,22] have reported similar observations. This correlates well with the difficulty encountered in separating adult heart muscle cell units. Apparently in the embryonic heart the muscle cells have functional activity but are loosely bound to one another. Separation of the individual cells was, therefore, possible.

Although the contracting CEHC are undoubtedly muscle cells, replacement of these cells by cells resembling fibroblasts when subcultures were made suggests that the original CEHC consisted of different types of cells, or that the muscle cells differentiated into fibroblasts, or both of these possibilities may have existed. The first appears to be more logical since pericardium and endocardium are not separated from the myocardium of the chicken embryo hearts before treatment with trypsin. Fibroblasts are probably the most vigorous of the cells grown in tissue culture and could well "overgrow" the muscle cells. Use of direct or indirect fluorescent antibody techniques to establish the presence or absence of myosin would be helpful.

A "network" of contracting CEHC fibers" occurred when degenerative changes produced cell-free spaces in the cell sheet. Many cells appeared to be compressed together to form a "fiber" (Fig. 1*B*). Conduction of contracting impulses was facilitated by this process, resulting in more vigorous contraction of the cells, and they tended to contract as one unit. The increased contraction after omission of essential amino acids or glutamine alone from the maintenance media cannot be explained by the foregoing mechanism, since it occurred without any visible cellular degeneration. The factor or factors found in glutamine or other essential amino acids which inhibit contraction need further study. As would be expected, a definite amount of calcium was required for contraction.

Study of the effect of certain viruses on heart cells was stimulated by abnormalities in cardiovascular physiology observed in man during the 1957 pandemic of influenza.[24] Only four of seven egg-adapted myxoviruses produced a cytopathic effect in chicken embryo heart cell cultures. The reason that influenza B/Lee, A/Swine, and C/N.O.1/60 produced no cytopathic effect was not apparent. None of the non-egg-adapted viruses were demonstrated to replicate or produce cytopathic effect (Table I).

Some of the contracting chicken embryo heart cells were destroyed by egg-adapted influenza A/PR8/34, A2/N.O.1/57, B/K 302/59, and parainfluenza 1 Sendai/52 viruses. The identical nature of the cytopathic changes in other types of chicken

embryo cells characterized the effect as nonspecific for heart muscle. Elimination of the cytopathic effect by previous inactivation (heating) or neutralization of the viruses together with failure to demonstrate replication suggested that the cytopathic effect was produced by one or more toxic properties residing in the active but nonreplicating viral units.

Although the cytopathic effect was nonspecific, most contracting chicken embryo heart cells were rapidly destroyed by the toxicity of the four viruses. It is easy to visualize a human-adapted strain of influenza or parainfluenza producing enough toxicity to cause myocardial failure or death in a patient, especially if the conduction tissues were involved. The mortality rate was higher in patients with cardiac diseases such as rheumatic heart disease with mitral stenosis when influenza was superimposed on their underlying condition in the recent pandemics (1957 and 1960). The nature of the effect of influenza and other viruses on the cardiovascular system in man certainly deserves thorough study.

Summary

Actively contracting chicken embryo heart cells were cultured in test tubes. Some of the contracting cells were observed to have cross-striations like those of cardiac muscle cells. Pilocarpine, strophanthin K, carbamylcholine, electrical stimulation, and omission of glutamine or other amino acids from the media stimulated contraction. Four egg-adapted myxoviruses (influenza A PR8/34, A2 N O 1/57, and B K302/59, and parainfluenza 1 Sendai/52) produced a cytopathic effect in chicken embryo heart cultures. This effect was not demonstrated to be associated with replication of the viruses, but was inactivated by previous heating or neutralization with antiserum. A similar cytopathic effect was produced by these viruses in cultures of other types of chicken embryonic cells, indicating that the cytopathologic change induced in chicken embryo heart cells was nonspecific. The ease with which large numbers of contracting chicken embryo heart cells can be cultured suggests that this experimental model may be useful in the study of the effects of infectious agents, toxins, drugs, and metabolic and nutritional changes on heart muscle.

Dr. Hugh J. Burford of the Department of Pharmacology assisted in performing the drug and electrical stimulation experiments.

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Case reports

Synchronization during electrical pacing

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It has been pointed out[1] that the co-existence of A-V conduction and an electronic pacemaker is in many ways similar to the interaction of two physiologic pacemakers. As in the physiologic situation, capture and interference dissociation occur. The possibility that true synchronization could occur under the circumstance of electronic pacing has likewise been mentioned but, to our knowledge, has not been reported previously without question or at least for any period of time. We have recently observed a patient who experienced several Adams-Stokes episodes, and who during pacing both by jugular bipolar and later by permanent (Medtronic) electrodes demonstrated the phenomenon of accrochage.

Case report

A 68-year-old white man had been told of "heart block" in 1952. A review of electrocardiograms from 1952 showed the presence of first-degree heart block and left bundle branch block. He remained asymptomatic until 1962, at which time he experienced several syncopal episodes, although none of these was witnessed by a physician. A full cardiac and neurologic work-up at that time was unrevealing except for the continued electrocardiographic finding of first-degree heart block. Past history was negative but for the presence of mild diabetes mellitus, discovered 6 or 7 years previous to admission, and treated sporadically with chlorpropamide. Treatment with small doses of atropine began in 1962, and no further symptoms were noted until Jan. 29, 1964, when three Adams-Stokes episodes occurred. He was hospitalized at New York University Hospital, where three more episodes were witnessed by the resident staff. At these times, atrial activity was seen on the cardiac monitor with 10 to 20-second ventricular asystoles. External pacing immediately ended the asystoles. Physical examination on admission revealed a youthful-appearing 68-year-old man who, except for syncopal periods, maintained a blood pressure at 146/80 mm. Hg and a slightly irregular pulse of 60 to 80 per minute. Pertinent findings included a faint apical systolic murmur and heart sounds of poor quality. There were no signs of congestive heart failure. The electrocardiogram did not show any changes when compared with the electrocardiogram from 1962, which was interpreted as showing first-degree block and left bundle branch block. Complete blood count and urine were within normal limits; serial transaminases were normal, as was the blood urea nitrogen. Fasting blood sugar was 103 mg. per cent. He was taken to the Cardiac Laboratory, where a bipolar pacemaker electrode (USCI) was passed into the right ventricular outflow tract via the right external jugular vein. At that point, it could be seen that the patient would respond at any voltage higher than 30 millivolts. Because of his relatively rapid rate (75 to 90 per minute at the time of insertion), there was much competition between pacemakers, and it was elected to allow the patient to pace on his own, with the electronic mechanism set to pace in emergencies only. There were no subsequent asystoles. The following day, when the pacer was again tried, it was noted that the pacer, set at any rate up to 75 per minute, would synchronize the patient's own atria (intrinsic rate 55 to 60 per minute) at the paced rate. Synchronization would cease as the ventricular rate was increased past 75 per minute, but, once the rate was synchronized below or at 75 per minute, it would remain synchronized for

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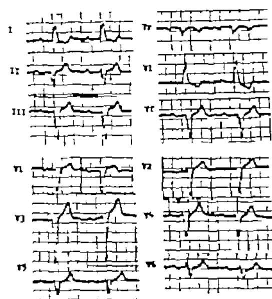


Fig. 1. Routine ECG before pacing demonstrates first-degree heart block (P-R 0.35 second in Lead II) and left bundle branch block.

indefinite periods. The P waves could be seen moving in both directions about the paced QRS, most frequently remaining in the neighborhood of the S-T segment and T wave. This phenomenon was noted at all times during this period. When the electronic pacer was stopped, the atrial rate would remain at the paced rate for a few beats, then slow to the intrinsic rate and mechanism. On Feb. 5, 1964, a permanent type of Medtronic pacemaker was inserted subcutaneously in the abdominal wall, and electrodes were implanted directly into the left ventricular musculature. The rate was set at 75 per minute. Recovery was uneventful. It was noted that much competition existed between atrial and paced impulses when the patient increased his intrinsic rate by exercise. At rest, the rhythm was entirely electrically paced, and accrochage was again seen to be present.

It should be noted that atropine was discontinued shortly after the patient was admitted to the hospital, as was sublingual Isuprel, which had been begun at the time of admission. No digitalis or quinidine was given at any time.

Discussion

The actual mechanism of synchronization is not known with certainty. The subject has been reviewed in detail by Marriott[2] and again by Schubart, Marriott and Gorten.[3] The phenomenon was first described by Gallavardin, and the name "accrochage" was applied by Segers.[4] The development of synchronization usually depends upon the acceleration of the slower rate to the faster one. It is most apt to occur when the two rates differ by no more than 25 per cent, and has been noted to occur at 2:1,[4] 3:1, 4:1, or even 3:2. Even when true synchronization does not occur, as in A-V dissociation and complete heart block, the independence of atria and ventricles is often not complete, as may be seen by noting that the observed P-P intervals (and P-R and R-P intervals) in these arrhythmias differ depending on the presence or absence of a QRS between two P waves.[5] Under these circumstances, it is noted that P waves tend to "cluster" about QRS complexes.

Segers[6] showed that two isolated frog hearts placed in contact tended to synchronize their rhythms, even if no anatomic connection existed between them when the two rates were close. That electrical interaction is not necessarily implicated has been demonstrated by successfully synchronizing two ventricles beating in a nonconducting medium (liquid paraffin). Rosenbaum and Lepeschkin[7] have suggested that mechanical traction on the atrium by ventricular contracture caused early occurrence of the following P wave in a case of complete heart block. If atrial and ventricular rates are close, synchronization might occur under these circumstances. Mechanical interaction has been postulated as the cause of synchronization, and additional credence is given to this idea by the demonstration of synchronization in nonconducting media. Grant[8] has proposed that the interaction may be electrical, and compared it to the relationship between two sensitive and easily disturbed coupled oscillators. It has been postulated[3] that since the P wave is most frequently seen following the QRS during synchronization the interaction is mechanical. However, this might apply as easily to the electrical effects of ventricular depolarization on the atria.

Since differing atrial and ventricular rates result in a progression of atrial and ventricular complexes relative to each other, criteria have been suggested[3] for recognizing true synchronization. In increasing order of probability, these are: (1) Atrial and ventricular pacemakers fall in step for a few beats. (2) A prompt return to synchronization follows after a disrupt

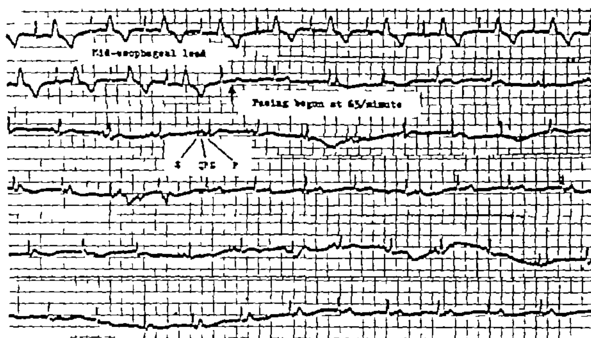


Fig. A continuous ECG strip taken from a mid-esophageal lead. The electronic impulses are seen as small nubbins preceding QRS of low amplitude in this lead. The P waves are tall and spiked in appearance. The electronic pacing is begun midway in the second strip. P is seen to "wander" to each side of the regularly occurring S-QRS complexes.

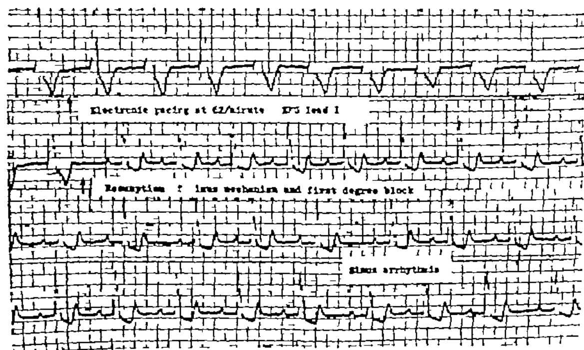


Fig. 3. A continuous ECG strip of Lead I. Pacing is regularly at 62 per minute and the electronic pacemaker is shut off in the second strip. Sinus mechanism is resumed with first-degree heart block and sinus arrhythmia.

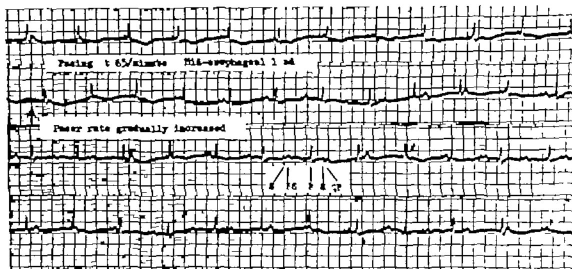


Fig. 4. A continuous strip, mid-esophageal lead. Pacing electronically is at 65 per minute; the pacer rate is gradually increased beginning in the second strip. The P waves begin to escape as paced rate exceeds 75 per minute, and dissociation occurs.

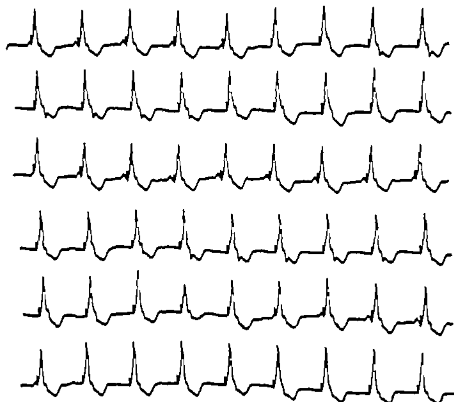


Fig. 5. Vectorcharge after implantation of permanent pacemaker. Rate of 75 per minute. Continuous strip. Synchronization is seen again, as P waves "wander" back and forth through QRS complexes. (The pacer impulses have been retouched here for visibility.)

ing event (premature beat or Valsalva maneuver) has occurred (3) When synchronized one pacemaker surrenders a feature of its identity such as an inherent arrhythmia

It is seen that these criteria were met by the present case Ventricular and atrial rates fell in step for long periods and thus occurred whenever pacing was started In addition the patient's marked sinus arrhythmia was seen to return a few beats after electronic pacing had ceased

Summary

The occurrence of synchronization (accrochage) of atria and ventricles during electronic pacing was noted in the case of a 68 year-old man treated for Adams-Stokes episodes The nature of this phenomenon is discussed and the mechanical and electrical theories of its etiology are mentioned briefly

Addendum

Since this article was submitted for publication it has come to my attention that this phenomenon has been observed elsewhere. A recent review of pacemaker rhythm phenomena[9] presents a similar case The present case is published to demonstrate that synchronization is not an isolated rare event but may occur more frequently than is generally realized during pacemaker competition

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The occurrence of mild coarctation of the aorta (pseudocoarctation) and coarctation in one family

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Dotter and Steinberg[1] in 1951 first described an anomaly of the aortic arch which they subsequently termed "pseudocoarctation." The malformation described consisted of constriction of the aortic isthmus with or without poststenotic dilatation of the descending aorta in the absence of evidence of hemodynamic compromise of the aortic lumen. There was, therefore, no difference in blood pressure between the upper and lower extremities, no collateral arterial circulation, no rib-notching, and no hypertension. The number of cases subsequently reported exceeds fifty. Various terms have been used to describe the condition: kinking, buckling, formes frustes, coarctation, and subclinical coarctation.[2-4] The purpose of this paper is to report the occurrence of mild coarctation (pseudocoarctation) and coarctation (true) in two brothers. Our preference for the term mild coarctation shall be explained.

Case histories

A. The patient, W. B., was a 32-year-old Caucasian male in whom an abnormality of the aortic arch had been discovered on a chest x-ray film taken during an episode of pneumonia at age 31. He denied symptoms referable to the cardiovascular system, although he did note that his legs easily became fatigued upon exertion. Physical examination disclosed the following blood pressures by cuff: right arm, 120/80 mm. Hg; left arm, 125/85 mm. Hg; right leg, 160/100 mm. Hg; left leg, 140/105 mm. Hg. The point of maximum impulse of the heartbeat was found in the fifth intercostal space at the mid-clavicular line. A Grade 2/6 systolic murmur was best heard in the second left intercostal space, and a Grade 1/6 systolic murmur was heard posteriorly at the tip of the left scapula. The aortic second sound was louder than the pulmonic second sound. The femoral pulses were full and equal to each other and greater than the radial pulses. Chest films showed an indentation in the descending aorta, and a double indentation of the barium-filled esophagus (Figs. 1 and 2). An electrocardiogram showed complete right bundle branch block. Retrograde femoral artery catheterization indicated no pressure gradient across the area of constriction (Fig. 3). The constriction was well seen in the descending aorta after the injection of 75 per cent Hypaque (Fig. 4). The diagnosis was mild coarctation of the aorta.

B. The patient's brother, R.B.,* came under medical care in 1961, at the age of 28, upon complaint of dyspnea, fatigability, and headaches. Hypertension had been discovered 7 months previously. Physical examination disclosed decreased femoral pulsations, chest films indicated notching of the ribs, and catheterization substantiated the diagnosis of coarctation of the aorta. Direct manometric pressure was 180/100 mm. Hg in the brachial artery and 110/90 mm. Hg in the femoral artery. The electrocardiogram revealed left ventricular hypertrophy. On Aug. 30, 1961, a large postductile coarctation of the aorta was found at operation. Resection was successfully accomplished, and the

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*The patient was cared for by Dr. Joseph J. [illegible], of Minneapolis, Minn., whom we wish to thank for [illegible] the case history available.

specimen showed a complete diaphragm at the level of the coarctation. Postoperative blood pressures were 178/90 mm. Hg in the right arm, and 174/120 mm. Hg in the popliteal area. Seventeen months postoperatively the blood pressure in the right arm was 184/100 mm. Hg and the pressure in the popliteal area was 160/110 mm. Hg. A bruit was heard in the right subcostal area and further study was advised in order to investigate the possibility of renal artery stenosis underlying the persisting hypertension. The patient did not return however.

Examination of W. B.'s three male children ages 2, 5, and 7 revealed no abnormality and their chest films and electrocardiograms were normal. It is of some interest that W. B.'s mother died in her early thirties of an unknown heart condition; an autopsy was not performed. The patient's two sisters, ages 32 and 34, were examined and had electrocardiograms and chest x-ray films that showed no abnormality.



Fig. 1. Lateral chest film showing indentation of the descending aorta.

Discussion

The distinction between coarctation and mild coarctation of the aorta anatomically is based upon the degree to which the aortic isthmus is constricted. Physiologically, the distinction is based upon the presence or absence of a pressure gradient across the compromised area. Gupta and Wiggers[3] determined that distal pressure does not significantly fall until the lumen of the stenotic segment is reduced to approximately 45 to 55 per cent of the cross-sectional area of the proximal aorta. In a review of autopsy specimens, Edmunds and associates[4] found all graduations of stenosis from mild to complete atresia. The finding of a difference in pressure between the upper and lower extremities, increased collateral arterial circulation, rib-notching, and the hypertension observed in coarctation of the aorta occur when there is more than a critical degree of occlusion of the lumen. Pulse pressure in the renal arteries has been thought to be an important factor in the causation of hypertension.[4] A degree of constriction sufficient to decrease distal aortic pressure is not present in mild coarctation. There may well be turbulence of flow as attested to by the murmur which is frequently present. Gupta[3] has found, in animal experiments, that murmurs can occur before demonstrable differences in pressure are observed. Turbulence of flow may, in addition to causing the murmur, lead to the development of poststenotic dilatation



Fig. 2. Posteroanterior chest film showing indentation of the descending aorta (*arrow*) and double indentation of the barium-filled esophagus.

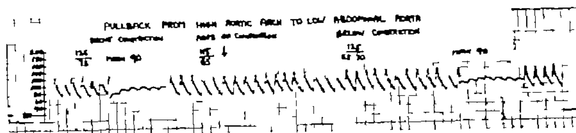


Fig. 3. Pressure tracing of retrograde femoral artery catheterization, showing no pressure gradient across the area of constriction.



Fig. 4. Aortogram showing constriction in the descending aorta (75 per cent Hypaque).

It has previously been suggested by Steinberg[7] that the two forms of coarctation are embryologically closely related. There are striking similarities between the two forms, including the location of the constriction, the presence and characteristics of the murmurs, radiographic appearances, and the presence of poststenotic dilatation. The occurrence of right bundle branch block is frequently noted in cases of coarctation, having been found by Ziegler[8] in 11 of 26 instances, and by Kjellberg and associates[9] in 17 of 53 instances. In view of this association it is interesting to note that our patient with mild coarctation was found to have complete right bundle branch block.

Accompanying cardiac anomalies have been reported with frequency in both forms. Steinberg[10] has described bicuspid aortic valve, aortic stenosis, aneurysm of the sinus of Valsalva, dextrorotation, and corrected transposition in patients with pseudocoarctation (mild coarctation). Campbell and Polani[11] in a series of 151 patients with coarctation of the aorta discovered 6 with aortic stenosis and 12 with malformations of a varied nature, an incidence twelvefold that predicted by chance alone. These authors also found a 7 per cent incidence of noncardiac malformations. The familial incidence of coarctation has been commented upon by Campbell and Polani. In their series, two sisters were found to have the lesion, and in other reports cited are instances comprising mother, son, and daughter, father and son, two brothers, and brother and sister.

The occurrence of mild coarctation and coarctation in siblings has not, to our knowledge, been previously reported. This finding would seem to favor a distinct genetic proclivity and similar embryologic mechanism in both forms of aortic coarctation. We believe that they differ in their manifestations only by virtue of the difference in the degree to which they constrict the aortic lumen. Therefore, we prefer the terminology "mild coarctation" and "coarctation." Coarctation refers to that form characterized by proximal aortic hypertension and diminished distal aortic pressure discoverable by decreased pulsation of the femoral artery. Mild coarctation, on the other hand, may be discovered only radiologically and perhaps by the presence of a murmur.

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Review

The carotid sinus reflexes

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In 1799 the Welsh physician Parry[1] wrote that he could often produce a temporary slowing of heart rate in his patients by strong pressure on one of the carotid arteries. Augustus Waller[2] reported a more detailed account of this event to the Royal Society (London) in 1862 but he thought that the bradycardia and decreased force of the pulse were due to irritation of the vagus nerve. And so too did Czermak[3] (1866) who succeeded in calling this observation to the general attention of physicians when he introduced *the vagus pressure test*. However Concato[4] (1870) reported in an apparently ignored communication that, in order to observe the bradycardia described by Czermak, pressure had to be applied in the region of the carotid bifurcation. Also Pagano[5] (1900) found that in animals the region of the carotid bifurcation was particularly sensitive to distention with various substances, such as nicotine or silver nitrate, and that bradycardia or cardiac arrest could be produced in this manner. Later Sollmann and Brown[6] (1912) caused hypotension by pulling caudally either the common or internal carotid arteries, but they failed to observe hypotension when the vagus was pulled. In spite of these observations, it was still the established belief until 1923 that pressure on the neck caused bradycardia and hypotension by irritating the vagus. On the other hand Astley Cooper[7] (1836) had observed that occlusion of the common carotid arteries caused an increase in systemic arterial pressure and he like others who confirmed this fact ascribed it to cerebral ischemia. Siciliano[8] in 1900 questioned this explanation, noting that the increase in blood pressure after occlusion of the common carotid arteries was much too rapid to be caused by cerebral ischemia. Indeed, he showed that occlusion of the vertebral arteries, the major suppliers of blood to the medulla, caused no significant change in blood pressure and neither was there any significant change in blood pressure after occlusion of the internal carotid arteries. He stated clearly that pressure on the walls of the common carotid arteries, although unfortunately he was not more precise about localization, was the important factor in the "autoregulation of the cerebral circulation." Siciliano's results were not confirmed by others,[9] and the established opinion continued to be that occlusion of the common carotid arteries caused hypertension and tachy

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cardia as the result of cerebral ischemia

Against this background Hering in 1923 1924 defined the reflex producing role of the carotid sinus in the circulatory system and this discovery immediately evoked intense efforts of research into the physiology and anatomy of the reflex.[1 12] Among other things, it was soon evident that the strength of the reflex varied greatly and could often produce especially in elderly and hypertensive persons severe hypotension bradycardia or asystole In deed several instances of fainting and con vulsions associated with marked circula tory changes were reported during me- chanical stimulation of the carotid sinus reflexes. It was logical therefore for the reflex to be studied as a possible cause of spontaneous idiopathic attacks of syn cope In 1933 Weiss and Baker[13] and later in 1935 Ferris, Capps and Weiss[14] made a detailed study of the association between spontaneous syncope and the activity of the carotid sinus reflex.

More importantly however much of the interest was generated by Hering's observation that the carotid sinus reflexes were tonically active and that if the sinus nerves were sectioned systemic hyperten- sion occurred Thus, the obvious implica tion that essential hypertension in man might be due to dysfunction of the carotid sinus and cardioaortic baroreceptor re flexes had to be investigated. During the next two decades investigators vigorously pursued this comparison between animal neurogenic and human essential hyper tension and it would seem to be fair to say that at the end of this time there was agreement that animal neurogenic hyper tension differed fundamentally from es- sential hypertension The neurogenic hy pertension produced by the techniques then in use was very labile and the increase in pressure was associated with tachy cardia and elevated cardiac output. If there were any correlation between animal neurogenic and human essential hyperten- sion it could only be made for the early labile period of the latter[11,15]

The conclusion that the baroreceptor reflexes had little or no role in the pathology of chronic hypertension was so definite that the large and increasing body of evidence to the contrary which has ap- peared from authoritative sources during the last 10 years has received less attention than it deserves Since 1954 workers have clearly demonstrated that permanent stable hypertension without tachycardia is readily produced in dogs by interfering bilaterally with the carotid sinus reflexes[16-19] In addition results from other recent in vestigations have renewed interest in the functions of the baroreceptor reflexes. For instance it has been shown that there is a relationship between the carotid sinus reflexes and renal (Goldblatt) hyperten sion to wit whether the reflexes are intact in the dog determines whether unilateral artery constriction produces permanent stable hypertension[20] Also it has been shown that in animals with chronic renal hypertension the carotid sinus barorecep- tor reflexes are reset at a higher level and the implication therefore exists that they may prevent the pressure from returning to normotensive levels, even though the original cause of the hypertension is removed[21] Finally most recently two groups of investigators one working with hypertensive dogs and the other with hypertensive patients, have shown that arterial pressure can be lowered for periods of at least several months by electrically stimulating the carotid sinus or a sinus nerve with an implanted pacemaker[22-24]

Carotid sinus reflexes in hemodynamic regulation

What is the role of the carotid sinus and aortic baroreceptors in hemodynamic regu lation? Actually the receptors of the re- flexes are not baroreceptors or pressor receptors but are stimulated by deforma tion of the sinus vascular wall Hauss, Kreuziger and Asteroth demonstrated this fact by encasing the carotid sinus in a plaster-of Paris cast and showing that increases in endosinus pressure *did not* then cause the usual reflex bradycardia and systemic hypotension.[25] Also the re- flexes are more sensitive to pulsatile endo- sinus pressures than to steady pressures Ead Green and Neil[26] showed that the reflex systemic hypotension caused by a given pulsatile endosinus pressure was greater than that caused by a steady pres- sure of the same mean value Bronk and Stella[27] had previously shown that the

numbers of fibers in the sinus nerve which were stimulated and their discharge frequency were greater at faster rates of change in endosinus pressure.

It is reasonable to assume that the carotid sinus reflexes are, in man, of major importance to hemodynamic regulation, for they are tonically active and if surgically interrupted a great increase in arterial pressure and heart rate will occur for periods of from 30 minutes to several weeks.[19,23-24] Present knowledge, almost all from animal studies, indicates that they act by affecting or buffering the outflow of autonomic nervous system activity from the brain and thus, increases or decreases in endosinus arterial pressure will respectively decrease and increase sympathetic cardiovascular activity; parasympathetic activity will be affected in the opposite direction.[27] If no attempt is made to place major emphasis on any particular effect of the carotid sinus reflex, it is possible to integrate the opinions of most investigators into a unified hypothesis of its role in hemodynamic regulation. This role would be that, when systemic arterial and endosinus pressure decrease the baroreceptors are stimulated less and the changes in the activity of the autonomic nervous system then tend to return the pressure to the original level. They do this (a) by decreasing the distensibility and volume of the postarteriolar capacity vessels, (b) by increasing cardiac work (1) reflexly through the autonomic nervous system (2) through intrinsic adjustments of the heart secondary to other changes in the circulatory system and (c) by increasing total peripheral resistance. It should be noted here that the above mentioned effects not only are caused by direct nervous action on the cardiovascular system but also are dependent in part on the increase in catecholamines in the blood.[27,31] Conversely, an increase in arterial pressure would stimulate the baroreceptors and cause effects in the opposite direction. When, however, an attempt is made to determine the relative importance of these different aspects of the baroreceptor reflexes, great difficulty arises.

What is the evidence that the baroreceptor reflexes affect the systemic postarteriolar capacity vessels? Since it is known that changes in sympathetic nervous activity and circulating catecholamines do change the distensibility of veins, it would seem to follow that the baroreceptor reflexes also could affect these vessels. The answer to the question is particularly relevant because these vessels contain approximately 70 per cent of the total volume of blood and even small changes in their capacity could significantly affect cardiac output and arterial pressure. Studies have shown that increased and decreased carotid sinus stimulation caused respectively increased and decreased distensibility of the mesenteric and saphenous veins.[33,44] Moreover, the shifting of blood volume to and from the systemic vascular bed caused by different levels of carotid sinus stimulation has been measured by various methods: extracorporeal reservoirs, major vessel occlusion technique, and during complete heart lung bypass. In three of four such studies the expected shift of blood in the animal was observed during carotid sinus hypotension and was in the opposite direction when endosinus pressure was raised.[41,42] The fourth investigation did not show changes in venous return to the heart during occlusion of the common carotid arteries.[44] However, all of the foregoing data on venous distensibility are results from experiments of short duration (minutes) in compromised animals (open chest, artificial breathing, deep anesthesia, etc.) and in the extracorporeal and heart lung bypass experiments there is no way of knowing what the distribution of the total volume of blood would be between the pulmonary and systemic vascular beds in the intact animals. On the other hand, in investigations of intact unanesthetized animals during acute bilateral occlusion of the common carotid arteries, large increases in systemic arterial pressure were associated with no change in cardiac output, in mean right atrial pressure, and no increase in intrathoracic blood volume (right atrium-aortic root).[43]

Also in our own laboratory, we have been measuring the hemodynamic changes in man caused by abolition of the carotid sinus reflex by the infiltration of lidocaine into the carotid sinus area, or stimulation of the reflex by the infiltration of epinephrine into the same area.[4] In these pro-

cedures large increases or decreases in systemic arterial pressure occur in the presence of only minor changes in mean and end-diastolic right atrial pressures even when cardiac output does not change Effective atrial pressures could not be measured because of a lack of knowledge of the intrathoracic pressures, but the depth and rate of respirations during the procedures usually did not change significantly

If however one assumes that the baroreceptor reflexes produce a significant reduction in the distensibility and volume of the postarteriolar capacity vessels, blood will be forced into the preventricular reservoirs of the large veins atria and pulmonary vascular bed This event by itself would increase end-diastolic fiber length and therefore stroke work. On the other hand it is known that changes in sympathetic and parasympathetic activity influence the work of the heart directly Indeed Sarnoff and Mitchell[17] have observed in dog preparations with constant heart rates that an increase or decrease in carotid sinus stimulation produced changes in stroke work in the expected directions, that is, decreases and increases, respectively The authors suggested that these results were due to reflexly induced changes in atrial and ventricular contractility and also to intrinsic changes in ventricular contractility secondary to the greater or lesser peripheral arteriolar resistance faced by the heart. Furthermore, they suggested that, in non paced animals, carotid sinus hypotension would increase ventricular contractility secondary to an increase in heart rate, and also that the reflexly induced shortening of systolic time and more rapid rate of ventricular relaxation would allow greater diastolic filling time a particularly important factor at high heart rates. However Salisbury and associates[17] showed that an increase in peripheral resistance alone (aortic compression) could cause the same effects as carotid sinus hypotension They concluded therefore that the expected reflex autonomic effects on the heart were not proved by the work of Sarnoff and associates and that the latters observations could have been due to intrinsic myocardial adaptation to increased arteriolar resistance as well as to the pacing of their preparations at high heart rates. A recent report by Gilmore and Siegel[18] answered this question by producing carotid sinus hypotension (common carotid artery occlusion) under conditions in which it was possible to maintain cardiac output and aortic pressure constant the latter objective was achieved by shunting blood from the femoral arteries to venous reservoirs during carotid artery occlusion These results showed that a decrease in carotid sinus stimulation caused a definite reflex increase in ventricular contractility

The results from specialized animal preparations in which some variables are kept constant do not necessarily answer the question of what is the normal integrated response of a complex hemodynamic reflex. Also because the intact animal or man has many adaptive mechanisms, the results from acute experiments must be extrapolated with reservation to more long term patterns of response.[19] What are the effects of the baroreceptor reflexes on cardiac output and peripheral resistance? There have been many acute experiments in cats, rabbits, and dogs, in which cardiac output has been measured with flowmeters or by the direct Fick and indicator-dilution methods.[41-52] Most of the studies have investigated the effects of decreasing carotid sinus stimulation usually by occluding both common carotid arteries for several minutes. In these experiments, in which there were considerable increases in systemic arterial pressure and heart rate there is disagreement as to whether cardiac output remains unchanged or increases. On the other hand there is reasonable agreement that it does not decrease As for peripheral resistance since it was calculated from the ratio of arterial pressure and cardiac output there was little agreement from the above mentioned investigations as to how it varied Two studies have attempted to measure cardiac output in reasonably intact animals with the direct Fick and indicator-dilution methods during stimulation of the carotid sinus reflex that is, by either electrical stimulation of the sinus nerve or elevation of endosinus pressure[53,54] These results showed either no change in cardiac output or a small −7 per cent, average decrease with a range from −23

to +34 per cent. The data would seem too few to warrant further analysis. The discrepancies in the data on cardiac output and peripheral resistance could be due to species differences and to differences in the design of the experiments but it is possible that some workers failed to take into account the fact that stimulation of the sympathetic nervous system by causing splenic contraction and an increase in hematocrit in animals, can influence the results from the direct Fick and indicator dilution methods.[34] Furthermore it must be questioned whether the direct Fick method can give reasonably accurate results during such acute experiments when there are presumably large variations in the consumption and blood saturation of oxygen Studies which measured cardiac output by reliable methods in chronically neurogenic hypertensive dogs are few and will be discussed later

What available data are there concerning the effects of the carotid sinus reflexes on cardiac output and total peripheral resistance in man? Weiss and Baker[41] used the indicator-dilution method to measure changes in cardiac output caused by external pressure on the carotid sinus. These measurements were made during syncope and convulsions in 4 patients and showed an average decrease of 29 per cent. In 1953 Kezdi[42] reported results from studies in which both carotid sinuses were anesthetized with procaine and in which the cardiac output was measured by the pulse wave method of Wezler and Böger He reported data from 1 normotensive and 2 hypertensive subjects which indicated that at the height of the very large elevations of blood pressure and heart rate cardiac output increased by nearly 100 per cent whereas peripheral resistance decreased to a varying degree In our laboratory we have also been making hemodynamic observations of the changes caused

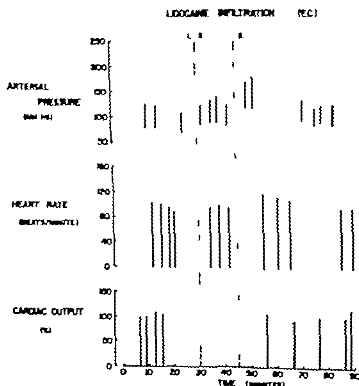


Fig. 1 Subject E.C. Bilateral carotid sinus anesthetization by infiltration of lidocaine. Compared with the average control values the maximum increase in arterial pressure of +49 per cent was associated with change in cardiac output (+4 per cent) and an increase in peripheral resistance of 44 per cent.

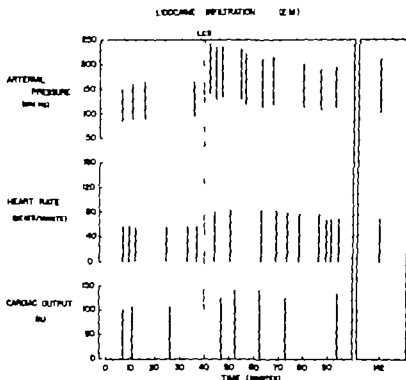


Fig. 2. Subject E.M. Unilateral carotid sinus anesthetization by infiltration of lidocaine. Compared with the average control values the maximum increase in blood pressure of +42 per cent was associated with an increase in cardiac output of +32 per cent and an increase in peripheral resistance of +8 per cent.

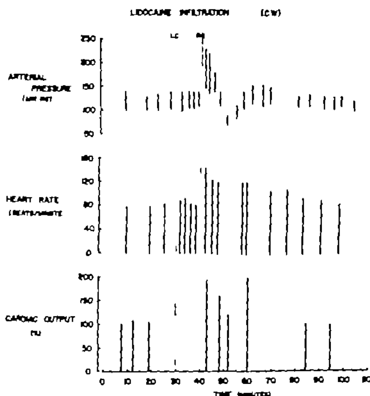


Fig. 3. Subject C.W. Bilateral carotid sinus anesthetization by infiltration of lidocaine. Compared with the average control values the arterial pressures varied greatly between +46 and −37 per cent. *During these changes* in pressure cardiac output increased between +20 and +100 per cent, and *the peripheral resistance decreased* between −24 and −50 per cent.

by blocking the carotid sinus reflex with local anesthesia.[49] In these studies, cardiac output has been measured by the indicator dilution method. We have studied nearly 40 cases and have been surprised by the differences in the individual responses of heart rate, blood pressure, cardiac output, and peripheral resistance. In some subjects with large elevations of blood pressure there may be no change in cardiac output and a large increase in peripheral resistance (Fig 1), a moderate increase in cardiac output and little change in peripheral resistance (Fig 2), or a large increase in cardiac output and a significant decrease in peripheral resistance (Fig 3). However, more studies are necessary before significant conclusions can be drawn, because the subjects' control blood pressures and ages varied widely, and because in some procedures only one carotid sinus was anesthetized whereas in others both were anesthetized. Also in several procedures we have reduced blood pressure and heart rate by the infiltration of epinephrine (50 to 100 γ) into the carotid sinus wall. Fig 4 shows the results from such a case in which blood pressure was reduced for several hours and was associated with no change of cardiac output and a large reduction in peripheral resistance. Also prior to the infiltration of epinephrine a change to the 45-degree head-up tilt position was associated with the expected decrease in cardiac output of approximately 20 per cent and a slightly larger increase in peripheral resistance.[44] Surprisingly, after the infiltration and during the period of reduced blood pressure, a similar tilt procedure was associated with no significant change in cardiac output or peripheral resistance. This type of study has particular relevance to the recent introduction of carotid sinus pacemakers.[33,34] It has been reported that hypertension in dogs and man can be reduced for at least several months by means of the electrical stimuli from permanently implanted pacemakers

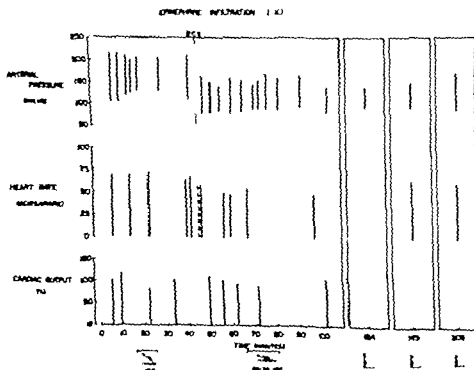


Fig 4 Subject J. K. Unilateral carotid sinus stimulation by infiltration of epinephrine (100 γ) into the carotid sinus wall. Compared with the average control values a decrease in arterial pressure of −31 per cent was associated with an insignificant change in cardiac output and a decrease in peripheral resistance of approximately −23 per cent. The effects of tilt are also demonstrated.

In the dog experiments an electrode on the heart is stimulated by the R wave and in this manner controls the delivery of bursts of electrical stimulation to the cardotid sinus. It has already been discussed that the carotid sinus reflexes may increase the capacity of the systemic postarteriolar vascular bed and decrease myocardial function and arteriolar resistance. Thus in human beings receiving constant carotid sinus stimulation it might have been expected that postural hypotension could occur from any one or a combination of these factors. Also it is interesting to consider whether the feedback mechanism used in the dog experiment would adversely affect their ability to meet demands for increased circulation of blood. For example in exercise the feedback mechanism could possibly interfer with the usual reflex adjustments, which decrease systemic postarteriolar capacity and increase heart rate and work and produce arteriolar constriction in nonexercising areas.[6] In any event the introduction of the carotid sinus pacemakers should stimulate greater research into the hemodynamic role of the baroreceptors.

Baroreceptor reflexes and hypertension

What is the relationship of the baroreceptor reflexes to hypertension in man? The earlier workers produced permanent neurogenic hypertension in most species of animals by a combination of complete bilateral carotid sinus denervation and partial vagotomy. In animals, some or most of the afferent fibers from the cardioaortic baroreceptors are intimately associated with the vagi and attempts to interrupt these fibers by partial vagotomy are necessarily associated with the destruction of vagal efferent fibers as well. Neurogenic hypertension so produced was singularly unlike essential or experimental renal hypertension. Environmental changes caused wide fluctuations in blood pressure which frequently was found to be normal when the animal rested quietly or was asleep. Furthermore the increases in systemic pressure were accompanied by considerable increases in heart rate and in a study in which the cardiac output was measured by the direct Fick method it was elevated from 30 to 50 per cent.[13] Also in a later publication Hawthorne and Mandal[14] reported results from 5 dogs in which chronic hypertension was produced by constriction of the brachiocephalic and left subclavian arteries close to the aorta. When compared with the values in 7 normotensive dogs the cardiac outputs of the hypertensive animals measured under pentobarbital anesthesia were approximately 100 per cent greater and the peripheral resistances were 75 per cent less. In spite of the authors conclusions, analysis of their data shows a large spread of cardiac index values from the 5 hypertensive dogs, the greatest being 150 per cent more than the smallest but much less difference in stroke index values. Therefore the increase in cardiac output in their dogs was closely associated with an increase in heart rate. Autopsy data from the earlier studies of chronically neurogenic hypertensive animals were conflicting but several authors reported cardiac hypertrophy myocardial fibrosis, aortic sclerosis, hyalinization and atrophy of renal glomerulli with or without interstitial fibrosis and renal arteriolitis.[13]

In 1954 Wakerlin Crandall and associates[16,17] reported that they were able to produce in dogs, permanent stable systemic hypertension of moderate to high levels by partial bilateral constriction of the carotid sinus area with small plastic clamps. The vagus nerves were left intact and the hypertension was not associated with tachycardia. These results have been confirmed by other workers.[18,19] It is now known that the clamp not only produces partial occlusion of the carotid sinus and bifurcation area but also probably destroys the innervation of the carotid sinus. Other recent investigations have shown that bilateral carotid sinus nerve denervation alone (vagi intact) without any occlusion of the carotid arteries will produce permanent stable hypertension without tachycardia.[19] At the moment there are conflicting results as to whether occlusion of the internal and external carotid (and occipital) arteries alone without carotid sinus denervation will produce some systemic hypertension. In any event cerebral ischemia is unlikely to be a factor in any of the above-mentioned studies, since in

the dog a major source of cerebral blood supply comes from the vertebral arteries, and abundant collaterals develop readily. The important point to consider however is that, contrary to the results reported during the first 30 years after Hering's discovery the work of the last decade is unequivocal in its conclusion that permanent, stable "carotid sinus hypertension" unassociated with tachycardia is readily produced in dogs.

Do the baroreceptor reflexes have any relationship to renal hypertension? There can be little doubt that the chronic phase of experimental renal hypertension is associated with considerable activity of the cardiovascular sympathetic nervous system.[67,68] In this regard Kezdi's latest observations deserve consideration. He showed that, in the dog the placing of a Goldblatt clamp on one renal artery caused only mild temporary hypertension, whereas when the procedure is combined with bilateral carotid sinus denervation a permanent, stable hypertension of moderate to high degree was produced.[69]

There is another possible relationship between the baroreceptors and renal hypertension. In 1956, McCubbin Green and Page[71] showed that in dogs with experimental renal hypertension the carotid sinus reflexes were "reset" at higher levels of arterial pressure than in normotensive dogs. That is, if a carotid sinus was subjected to increasing levels of steady or pulsatile endosinus pressure from a pump the stimulation of the reflex, as monitored by direct electroneurograms from the sinus nerve began at substantially lower pressures in the normotensive than in the hypertensive dogs. These results imply that once the reflexes were reset, they would act to maintain the blood pressure at the elevated level even if the original cause of the hypertension disappeared. This explanation could be relevent to cases in which blood pressure does not return to normotensive levels after unilateral renovascular repair or nephrectomy removal of a pheochromocytoma, or after delivery in instances of toxemia of pregnancy. Unfortunately McCubbin and associates used for their study only hypertensive animals which had mean blood pressures of at least 200 mm.Hg. If the resetting were secondary to changes in the elasticity of the carotid sinus wall and/or direct receptor dysfunction then it could be questioned whether the carotid sinus of hypertensive animals and man subjected to less severe pressure stress would also show resetting. Furthermore it is possible that the changes in carotid sinus sensitivity seen by these authors were due at least in part to hormonal and/or electrolyte changes associated with renal hypertension. If this were the case it could reasonably be expected that if the chemical millieu changed i.e., if the original cause of the hypertension were removed and the carotid sinus reflexes were not irreversibly damaged they would become more sensitive. Kezdi[69] attacked this question by partially isolating the carotid sinus in renal hypertensive dogs so that, although the reflexes were not exposed to the systemic hypertension they were subjected to the hormonal and electrolyte changes of the body. The carotid sinus reflexes in these animals were not reset at higher levels than in normotensive dogs. Unfortunately this study could not rule out the possibility that the decreased sensitivity of the carotid sinus as demonstrated by McCubbin Green and Page was the combined result of *both* high endosinus pressure and hormonal and/or electrolyte changes.

Is there evidence of the resetting of baroreceptor reflexes in man? In animals it is known that more than 6 hours of hypertension are required to establish baroreceptor resetting.[71,67] If it occurs in man it must be established very slowly. For instance unilateral or bilateral carotid sinus denervation is frequently followed by systemic hypertension for periods of days to several weeks, but the pressure then returns to the preoperative levels. Also in pregnancy blood pressure can be elevated for months and then it often descends immediately to normotensive levels after delivery. Furthermore it is a common clinical experience that chronic hypertensive patients may experience very large reductions in arterial pressure after 2 or 3 days of a hospital stay. However it must be admitted that without electroneurograms from the sinus nerve the question of whether baroreceptor rese

exists in man cannot be adequately answered from changes in blood pressure measurements alone. For example a patient with toxemia of pregnancy whose pressure decreases immediately after delivery may still have reset baroreceptors. In such a situation the decrease in blood pressure might be secondary to a reduction of cardiac output.

If the baroreceptor reflexes have an important role in human hypertension, it would seem most likely that the question will ultimately be answered from the data gathered in procedures involving human beings themselves. Directly recorded or telemetered electroneurograms from the sinus nerve combined with computer analysis of these records, could answer most of our present questions. Meanwhile data obtained directly from man allow us to make some assessment of the part played by baroreceptor reflexes in essential hypertension. Clearly if the function of these reflexes is to keep blood pressure at *normal levels, it must be asked whether* they are functioning at all? And if so are the reflexes working at their maximum capabilities? The answer to the first question is unequivocally yes, and to the second unequivocally no. When the carotid sinus reflexes of hypertensive patients are interrupted by either surgical denervation[13,22] or infiltration of the wall of the carotid sinus with a local anesthetic[11,20] there is a large increase in arterial pressure. Therefore the reflexes are working and do seem to have a part in keeping the pressure of the hypertensive patient from being even higher. On the other hand the reflexes are not working to their full potentialities. For example stimulation of even one carotid sinus by external pressure will cause a large decrease in arterial pressure *in many* hypertensive patients. Also infiltration of small quantities of epinephrine into the wall of the carotid sinus will stimulate the reflex and cause dramatic decreases in arterial pressure[19] (Fig. 4). Finally recent reports by Griffith and Schwartz[24] that the blood pressure of hypertensive patients can be reduced for at least several months by electrical stimulation of one sinus nerve provide clear confirmation that not only are the reflexes not working maximally but that also the capability of a single baroreceptor reflex is great enough *to maintain* blood pressure at normotensive levels. However the question of whether the baroreceptor *reflexes are functioning normally in* hypertension cannot now be answered. To do that one must first consider whether inhibition of these reflexes with local anesthesia or stimulation of them by external pressure, infiltration of epinephrine or electrical current causes *abnormal degrees* of response.

Regardless of whether baroreceptor malfunction is a *major factor in human hypertension* data now available indicate that permanent increases in blood pressure do not result after *unilateral or bilateral* carotid sinus surgical denervation.[13,14,23-25] Such procedures have been carried out as treatment for the carotid sinus *syndrome* epilepsy progressive muscular dystrophy and glossopharyngeal neuralgia (the sinus nerve is a branch of the glossopharyngeal nerve). Also the denervation has necessarily *been associated with surgery for* radical dissection of the neck and that involving prosthetic replacements of occluded carotid vessels. *After interruption* of the carotid sinus reflexes there are considerable increases in blood pressure and *heart rate but they have been reported* to return to the preoperative levels within periods of 20 to 40 minutes, several hours, days and even weeks. The procedures have been reported in young old normotensive and hypertensive patients. Indeed case histories are available from 2 moderately severe hypertensive patients who were subjected to bilateral carotid sinus denervation.[13,22] Perhaps the most likely interpretation of the return of the arterial pressure to preoperative levels is that the other baroreceptor reflexes increase *their influence* and *take over.* Nevertheless, it is interesting to compare this slow reduction in pressure of hours to weeks with the immediate response of the carotid sinus reflexes to anesthetization with procaine or external pressure infiltration of epinephrine or electrical stimulation. This discrepancy could indicate that these types of inhibition and stimulation of the carotid sinus are extreme and unphysiological. *Another explanation of* this discrepancy would be that the carotid

sinus reflexes are faster-acting than the other baroreceptor reflexes. On the other hand it is possible that the slow decrease in arterial pressure after carotid sinus denervation does not represent an increase in the power of the other baroreceptor reflexes at all This possibility must be considered because of the difficulty of drawing hemodynamic conclusions from the measurements of changes in blood pressure alone. It is conceivable that the other reflexes did not increase their tonic activity and that the reductions in blood pressure and heart rate after carotid sinus denervation were secondary to nonreflex changes in myocardial activity total blood volume, and to reduced cardiac output

Ask Upmark and Fajers[71,72] emphasized the observation that patients with the aortic arch syndrome" or pulseless disease" (Takayashu s syndrome, syphilitic aortitis severe atherosclerosis, etc.) frequently have severe hypertension in the nonoccluded vessels. This is particularly significant in Takayashu s syndrome since the patients are usually young Because of the locations of the pathologic lesions, it would seem that the baroreceptor reflexes should receive serious consideration as a major element in the etiology of the hypertension. On the one hand it could be expected that the carotid sinus receptors would be stimulated less because (a) pulse and mean pressures might be less in the *carotid sinus distal to the occlusion* of the brachiocephalic vessels and (b) the walls of the carotid sinus would be relatively rigid from the disease process, and their response less to the expanding stimulating forces. On the other hand the aortic baroreceptors would also be affected by the disease process which would make the walls of the aorta and large vessels arising from the aortic arch more rigid Scar tissue in these regions could also compromise nerves arising from the receptors. Thus, the hypertension could be due to attenuation of the influences of all four major baroreceptor areas. Also the pathologic situation is similar to that set up by some workers to produce hypertension in animals. It could mimic either the experimental design of Hawthorne and Mandal[44] in which the hypertension was produced in dogs by partially occluding the barchiocephalic and left subclavian arteries close to the aortic arch or that produced by Wakerlin and associates[14,17] with a plastic clamp on the carotid sinus areas. In both instances in addition to decreased baroreceptor stimulation the effects of altered cerebral hemodynamics must be considered[14,72]

Carotid sinus syndrome

Does the carotid sinus syndrome exist That is, are spontaneous attacks of syncope caused by stimulation of carotid sinus receptors? (The carotid sinus syndrome can refer to dizziness, weakness, syncope and/or convulsions, but in the following discussion we shall use only the term *syncope* although any or all of the other terms could be substituted for or used with it) It is quite infrequent for a patient to incriminate for his spontaneous attacks of syncope any direct and immediately apparent causes of stimulation of the carotid sinus area, such as direct pressure, a tight collar shaving or scratching[18,23,11,73,75] Most investigators include rapid turning of the head among these immediately apparent causes of the spontaneous attacks. This would seem to be highly speculative without further data since the act might cause syncope by other means, such as dysfunction of the inner ear or cranial nerve tension Therefore most diagnoses of carotid sinus syndrome are based on the association of (a) spontaneous attacks of syncope with (b) the production of qualitatively *similar* types of syncope by direct pressure over the carotid sinus but *not* by the application of pressure over the ipsilateral common carotid artery *If syncope* occurs during the latter maneuver the syncope previously observed during stimulation of the carotid sinus is then attributed to cerebral ischemia and not to the reflex.

No one would deny that, if syncope *were produced after the application of* pressure to both the carotid sinus and common carotid artery it would be due to reduced cerebral blood flow However if pressure on the common carotid artery does not cause syncope one cannot accept this as proving that syncope associated with carotid sinus pressure is due to stimulation of the reflex For it is likely

that investigators while stimulating the carotid sinus occlude at least partially the internal carotid artery Some make efforts to reduce occlusion of the artery by pressing gently or intermittently but many press very firmly as did Weiss and coworkers bulbar dilation (carotid sinus) held firmly over the cervical spine using fairly *strong* pressure with gentle massage.[14] Therefore in most instances in which syncope is produced by carotid sinus pressure a reduction in cerebral blood flow presumably occurs and is the result of two effects (a) partial or complete occlusion of an internal carotid artery on the side of carotid sinus pressure and (b) a reduction of flow in the vertebral basilar artery system and the contra lateral internal carotid artery secondary to generalized systemic hypotension

Pressure on the common carotid artery cannot reliably estimate the amount of occlusion of the internal carotid artery which occurs during carotid sinus pressure tests. Sweet and associates[76,77] showed that although there is no significant flow of blood from the ipsilateral external to internal carotid arteries during occlusion of the common carotid artery under direct vision at the time of operation percutaneous common carotid artery pressure was a very uncertain method for reducing directly recorded internal carotid artery pressure However the great fallacy of comparing the effects of carotid sinus and common carotid artery pressure in order to make the diagnosis of carotid sinus syndrome is that the reduction in cerebral blood flow which may be caused by mechanical obstruction *during pressure on the common carotid artery* occurs in the presence of unchanged general systemic arterial pressure or as is more likely if the compression is effective and there is a decrease in pressure in the ipsilateral carotid sinus it occurs in the presence of an elevation of systemic pressure. Therefore blood flow in the vertebral basilar artery system and the contralateral internal carotid artery is either unchanged or actually increased On the other hand obstruction of flow in the internal carotid artery *during pressure on the carotid sinus* is associated with decreased flow in all other blood vessels supplying the brain secondary to systemic hypotension As long as there is a possibility that partial or complete occlusion of the internal carotid artery occurs during the carotid sinus pressure test the possibility that carotid sinus syncope is due partially to this occlusion cannot be ruled out by pressure on the ipsilateral common carotid artery

The abolition of the baroreceptor reflex by infiltration of procaine into the carotid sinus area is also of no help in making the diagnosis of carotid sinus syndrome. After the infiltration of procaine there is no reflex systemic hypotension when the carotid sinus is pressed and occlusion of the internal carotid artery is unaccompanied by reduced flow in the other major cerebral vessels. In making the diagnosis, it would be possible to eliminate the artifact of occlusion of the internal carotid artery by electrically stimulating the sinus nerve under direct vision and reducing systemic pressure quickly and to the same level as that observed during carotid sinus pressure.[71] Nevertheless, even here, if the patient experienced syncope during electrical stimulation this would not prove that his spontaneous syncopal attacks were due to stimulation of the carotid sinus, since they could be due to any other condition producing rapid hypotension

When syncope occurs during carotid sinus pressure, it is classified as cardiac (vagal) depressor (vasomotor) or cerebral.[12,14,27] It is claimed that there are pure types, and results have been reported according to which ventricular asystole lasted for 7 to 10 seconds with little or no reduction of blood pressure These reports are even more surprising since the blood pressures were taken by the auscultatory method during the period of asystole Presumably the pressures reported were obtained several seconds after the release of carotid sinus pressure or after vagal escape. Investigations in which continuous recordings of intra arterial pressures have been made indicate that marked bradycardia or asystole during carotid sinus pressure was always associated with marked hypotension.[12,78] The pure type of vasomotor syncope, that is marked hypotension unassociated with

changes in heart rate is exceedingly rare.[13,14,72,73,79]

The cerebral type of syncope has been attributed to a direct reflex independent of reduced total cerebral blood flow. The efferent arm of the reflex, it is proposed, produces either localized cerebral vasoconstriction (and) or direct stimulation or inhibition of a center controlling consciousness.[14] We are unaware of any reports of a pure cerebral type in which continuous readings were made of the intra-arterial blood pressure.[73,75,79] Before the designation of cerebral type can be made, the possibility must be ruled out that these patients are unable to tolerate unilateral occlusion of the internal carotid arteries and minor general systemic hypotension *with consequent reduction of* cerebral blood flow in the other arteries to the brain. That a reduction in total cerebral blood flow is the cause of the cerebral type of syncope is indicated by the fact that it can rarely be produced in the recumbent position.[14]

If the syncope is not "pure," atropine and epinephrine are used to determine the predominant type of the syncope.[13,14,73-75,80] If, for example, during the initial test the syncope is associated with marked bradycardia or asystole *and marked hypotension*, 1 to 2 mg. of atropine is then given parenterally and the test is performed again. If after this there is no change in heart rate during carotid sinus pressure and no syncope, the previous syncope is said to have been of the vagal type. If, however, after the administration of atropine, carotid sinus pressure still causes syncope and hypotension, parenteral epinephrine is given (approximately 0.5 ml. of 1:1000 aqueous solution). If the syncope is abolished, it is called vasomotor in type. If syncope still occurs after both atropine and epinephrine without accompanying "significant" changes in systemic pressure, it is said to be cerebral in type. It is noted that most of the cerebral types of syncope reported by Ferris, Capps, and Weiss[14] were not "pure" and their designation depended on using the above-mentioned drugs.

It must be seriously questioned whether the classification of carotid sinus syncope into cardiac, vasodepressor, and cerebral types can be made by the above-mentioned methods. Essentially, the classification implies a differentiation of the effects of carotid sinus stimulation on cardiac output and peripheral arteriolar resistance. However, only heart rates and blood pressures are measured during carotid sinus pressure tests. Except during ventricular standstill, when heart outflow is zero, heart rate alone is an unreliable guide to cardiac output and, therefore, adequate interpretations of changes in blood pressure during stimulation of the carotid sinus cannot be made. More specifically, heart outflow is influenced by many factors independent of changes in heart rate and, for example, it is highly probable that in many instances carotid sinus *stimulation reduces the outflow by reducing* venous return and myocardial function.[37,42]

It is also not immediately apparent how atropine and or epinephrine can help in establishing a valid classification of carotid sinus syncope. In the parenteral doses usually employed in these tests, atropine causes large increases in heart rate and cardiac output and a large decrease in peripheral resistance.[81] Epinephrine causes changes in the same direction.[82] *Clearly, it would be difficult to* compare the changes caused by carotid stimulation before and after the administration of these drugs when the control values (i.e., before carotid sinus pressure) of cardiac output and peripheral resistance would be so radically different. In any event, monitoring of only heart rate and blood pressures cannot determine whether arteriolar vasodilation or a decrease in heart outflow is the more important element with reference to changes in blood pressure during carotid sinus stimulation.

Regardless of the mechanism by which *carotid sinus syncope* is produced, how is it possible to make the diagnosis of *carotid sinus syndrome?* It would seem to be a reasonable diagnosis in persons who give a history of repeated spontaneous syncopal attacks brought about by events clearly related to pressure on a carotid sinus area or areas, and in whom carotid sinus stimulation by external pressure, quantitatively similar to that which brought on the spontaneous attacks, also causes syncope.

The diagnosis is even more probable in persons who have the above-mentioned qualifications, and who also present on physical examination significant masses (nodes, tumors, scar tissue) or vascular deformations (aneurysms) in the carotid sinus region. However, even here the diagnoses could be missed because of the position of the body during the test. Spontaneous attacks of syncope in a person with the carotid sinus syndrome nearly always occur when the person is in the sitting or the erect position. Therefore, the test could be negative in a person in the recumbent supine position, especially if pressures are used which are quantitatively similar to that which occurs in the spontaneous attacks, rather than firm pressures of long duration. If the test is performed with the person in the erect or sitting position, it is not without danger, but if his symptoms are severe enough to warrant consideration of definitive surgical therapy, there would seem to be no alternative.

However, the great majority of patients with the diagnosis of carotid sinus syndrome have no history of obvious stimulation of the carotid sinus. The diagnosis is made on the basis of a history of spontaneous syncope and the tests described previously. Since these tests are inadequate, it is difficult to see how this can be done with any degree of certainty preoperatively, that is, before carotid sinus denervation. If the spontaneous attacks cease after surgical denervation, the diagnosis is presumably made. Unfortunately, even here there are areas of uncertainty. Many of these patients are neurotic, and this makes interpretation of the postoperative results difficult. Nevertheless, carotid sinus denervation is successful in many cases, and indeed in the majority of published cases.[12,14,19,24] But successful denervation does not prove that stimulation of the carotid sinus reflex which was interrupted by surgery was the only cause of the spontaneous syncopal attacks. There are many events and reflexes which can together cause hypotension and, therefore, the removal of any important element in this complex could decrease its capacity to lower cerebral blood flow to the syncope threshold. Thus, one is forced to conclude that, without further investigations, the diagnosis of carotid syndrome, in most cases, cannot be made either by the tests presently employed or from the results of surgical therapy.

Summary

Forty years have elapsed since Hering defined the carotid sinus reflex. Present theory indicates that the reflexes act by "buffering" the outflow from the brain of sympathetic and parasympathetic nervous system activity. Through changes in this autonomic nervous system outflow, decreases in systemic arterial pressure would be opposed by (a) decreases in the distensibility and volume of the systemic postarteriolar capacity vessels, (b) increases in cardiac work, and (c) increases in total peripheral resistance. Conversely, increases in arterial pressure would be opposed by effects in the opposite direction.

Until the last decade, baroreceptor experimental neurogenic hypertension was produced by bilateral carotid sinus denervation and partial vagotomy. The hypertension so caused was singularly unlike essential hypertension. It was very labile, and the increase in arterial pressure was associated with tachycardia and an elevation of cardiac output. However, since 1954, it has been clearly demonstrated that permanent, stable hypertension without tachycardia can readily be produced in dogs by bilaterally interfering with the carotid sinus reflexes alone (vagi intact). Furthermore, it has been shown that the carotid sinus reflexes may be of significance in the production of renal hypertension. Also, carotid sinus pacemakers have recently been shown to be capable of reducing blood pressure in hypertensive dogs and man.

It has been held for more than 30 years that spontaneous syncopal attacks are caused by stimulation of the carotid sinus reflexes. Nevertheless, in the great majority of patients with a diagnosis of carotid sinus syndrome, spontaneous syncope is not associated with an immediately apparent stimulation of the carotid sinus, such as direct pressure, a tight collar, shaving, or scratching. It is argued in the present communication that in those cases without apparent stimulation of

the carotid sinus the diagnosis of carotid sinus syndrome cannot be made or classified by the tests presently employed Even the results of surgical denervation cannot prove the existence of the carotid sinus syndrome in most cases

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The psychologic management of patients with cardiac disease

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The experienced physician knows that of the various symptoms associated with disorders of the heart, fear causes more hours of human suffering than all of the others combined. Fear may endure not for minutes or hours, but for months or years. It strikes not only the patient but also his family and sometimes his friends. It may likewise affect the physician.

The doctor's fear. At the *conscious level* intellectual concern for the patient is good whereas emotional alarm is the reverse because it may impair judgment. But it is when *subconscious* fear for his own reputation enters the doctor's mind that evil effects are most likely to ensue. These include excessive precautions and unnecessary restrictions, prescribed *not* for the patient's benefit but because the physician might otherwise be criticized if death should occur. The remedy for this is for the doctor to have that serenity of mind and justified confidence in his own judgment that can come only from a thorough comprehension of the disease and a wise understanding of the patient's personality.

The patient's fear. The feelings of many persons with cardiac disorders, whether grave or innocent, were expressed by Coleridge in *The Ancient Mariner.* The patient may be

> Like one that on a lonesome road
> Doth walk in fear and dread
> And having once turned round, walks on,
> And turns no more his head
> Because he knows a frightful fiend
> Doth close behind him tread.

The terrified patient, not realizing that *the pursuing fiend is often no more than a wisp of vapor,* is likely to assume that he is being stalked by the pale horse of Death. The spectrum of fright may range from completely justified fear, e.g., the still conscious patient with progressive pulmonary edema and circulatory collapse consequent to massive myocardial infarction, *to totally unnecessary* fear due to overwhelming anxiety consequent to the palpitation induced by innocent premature beats. Such terror becomes all the more tragic when it is mainly of iatrogenic origin, induced by erroneous statements based not on callousness but on ignorance, combined with the doctor's excessive concern for his own reputation. Aside from mistakes, fortunately rare, due to defects in the physician's integrity, the most serious error that can be made is that of a false-

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positive diagnosis of heart disease, because of its inherently uncertain prognosis.

Between these two extremes of totally justified and completely unjustified fear there are all gradations. One of the common problems is that of the young woman who has structural heart disease with no impairment of myocardial reserve. She is likely either to be inherently unstable or to have certain marital or personal tensions. The tragic and unnecessary sequence of events is indicated in Fig. 1.

The iatrogenic component of this vicious cycle has been the conversion of alarm into terror and the induction of the hallucination that every whisper of the wind represents the clicking of the shears of Atropos, that most implacable of the Fates whose function was the severance of the thread of life.

This single example, which could be supplemented by scores of others, leads us to what may be called the first principle in the management of heart disease. *The physician should avoid creating fear by his words or acts and should attempt to combat it by every reasonable means.* His first concern should be the relief of suffering, with the full realization that our inability to express such phenomena as pain and fear in physical or chemical units does not imply their biologic insignificance. Here, as in so many medical problems, measurement must yield to judgment.

The physician should teach his patient that *there is no parallelism whatever between the gravity of a symptom and the amount of fright which it induces.* Thus, anginal pain, even when minimal and a source of no concern to the patient, is always accompanied by the possibility of sudden unexpected death, whereas palpitation is likely to cause alarm or even terror even though it is commonly the most benign of all symptoms related to the heart.

In many situations the *simple truth* stated with tact and wisdom is the doctor's best weapon. Most of us tend to fear that which is strange and to discount the significance of the commonplace. Thus, a mythical dragon seen only in a nightmare is likely to inspire even more terror than an existing lion. One method of combating fright is the attempt to *convert the unfamiliar into the familiar* by a suitable and truthful analogy. The comparison of heart disease with the automobile is frequently fruitful.

Almost every layman is familiar with the annual death and accident tolls from the motor car in the United States (about 40,000 persons killed, about 100,000 permanently maimed, and about 4,000,000 slightly or severely injured). After citing these statistics, the physician may continue, "Now, if your only knowledge of the automobile was derived from these figures plus what you read in the newspaper, which tells of persons involved in serious accidents but not of those who drive 300,000 miles without scratching a fender, then you as a rational person would draw only one conclusion. You would probably say to yourself, 'I'll never go near one of those things.' But your knowledge is not so limited. You *are* familiar with cars. You know that, if you drive properly, you cannot eliminate the hazard entirely, but that you can reduce it to a risk which you are content to take."

"Now, let's consider heart disease. You are aware from the newspaper and other sources that the number of fatalities is large. But you probably do not know that for every person with heart disease who dies there are many who live happy and useful lives for years and often for decades.

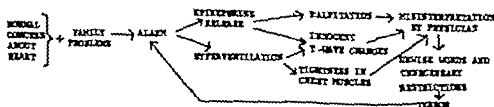


Fig. 1. Sequence of events in the production of fear in a patient with cardiac disease. See text.

despite the presence of definite and even advanced structural disease of the heart. Thus it is your unfamiliarity with heart disease which produces your alarm If you tell me that you are totally unwilling to either drive or ride in a car because of the hazard involved I will concede that your anxiety about your heart has a rational basis. Otherwise I agree with you that it is an occasion for concern but disagree that it justifies alarm Actually the figures show that when the average person with heart disease is on the highway in his car the hazard of sudden death from his car is at least as great as and probably greater than that from his heart The risk of becoming a lifelong bedridden or wheel-chair invalid is much greater from the car

Let's carry the analogy further We agree that no matter how carefully you drive you cannot completely escape the hazard of the auto Some fool may smash into you Neither can I completely eliminate the hazard from your heart But I can reduce it by teaching you how to manage it wisely This does not mean invalidism On the contrary I want you to go fishing or play golf or

These quotations from the advice of a hypothetical physician to an imaginary patient will not apply to every doctor or to every person with cardiac disease Each physician will need to combat apprehension according to his own particular methods, which will obviously vary from one patient to another The emphasis here is not on the technique of reassurance but rather on three principles i.e *the conversion of the unfamiliar to the familiar hazard* stress, not on the presence or absence of risk, but *on the degree of risk* and *the therapeutic value of the truth* when wisely stated

These reflections do not imply that every patient with cardiac disease is to be bluntly told the complete unvarnished truth. What the wise doctor says will vary from patient to patient, from relative to relative and from one disease picture to another

The *importance of properly regulated and prescribed physical activity in overcoming fear* cannot be overemphasized Although patients know that a doctor does not always tell the complete truth they also know that he will never give advice that he considers to be harmful Therefore a physician's positive direction to undertake certain physical activities, such as fishing or golf is likely to be far more reassuring than any encouraging thing he may say about the probable future outlook. The activity prescribed will necessarily vary with the type of heart disease its functional severity and the age and tastes of the patient In many persons mild subsymptomatic physical exertion promotes appetite and sleep and the resulting slight physical fatigue is often the best antidote for emotional stress *Physical activity prescribed by the physician restores confidence*

Summary Dangerous disorders which threaten life and serious disorders which threaten happiness are not the same Death is inevitable its occurrence before one's expected time is, at worst only a quantitative tragedy But misery of spirit lasting for decades is not inevitable its occurrence at all is a qualitative tragedy

Sedatives and tranquilizers have their proper place as weapons against fear but are far inferior to the wise physician He by his words, actions and feelings can do much to banish this most common and most distressing of the symptoms related to disease of the heart. He must avoid the mistake of binding a vigorous Prometheus to the rock of Misery with chains of Fear forged either by a false diagnosis of structural heart disease or by an erroneous evaluation of its functional significance Neither the electrocardiogram the fluoroscope, nor the cardiac catheter can tell the physician what to say or how to say it Science is no substitute for wisdom

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Antiarrhythmic drugs
Part III. Quinidine toxicity

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The use of quinidine in the treatment and control of arrhythmia has always been associated with significant morbidity and a definite mortality risk, despite the most conscientious and informed control of dosage. The wide range in individual dose requirements and drug tolerance makes this unavoidable. In a series which included desperately ill patients in shock and patients in whom (in the absence of any alternative therapy) very high doses were used, the mortality was reported as 2 per cent. The risk under usual circumstances, with a smaller dose, would be considerably less. The toxic manifestations of quinidine are of several types and involve many organs.

Toxicity due to allergy. True allergic reactions, reflecting sensitization after prior exposure to the drug, are not uncommon, although usually not life threatening. Skin eruptions have been reported, as well as drug fever both with and without associated skin eruptions. Serious episodes of thrombocytopenic purpura have been produced by quinidine. In this instance quinidine acts as a hapten and combines with the patient's platelets to form an antigen to which antibody is produced. When quinidine is again administered, the antibody binds to the quinidine-platelet complex, and, in the presence of complement, produces lysis of platelets and clinical purpura. A hemolytic anemia has also been produced by quinidine through a similar mechanism. A test has recently been described in which quinidine can be identified as the offending agent in vitro even during the acute episode. The test is based on the prevention of clot retraction in blood of another subject when small amounts of quinidine and the patient's serum are added.

Toxicity due to idiosyncrasy. Far more common than allergic reactions is idiosyncratic intolerance to relatively low doses of quinidine manifested by symptoms either in the gastrointestinal tract or the central nervous system. The most common reason for the discontinuance of quinidine therapy is the development of gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Since, unlike the situation with digitalis-induced gastrointestinal symptoms, symptoms due to quinidine are not closely correlated with cardiovascular toxicity, it is reasonable to treat these reactions symptomatically when the patient's distress is not severe and to continue the administration of quinidine if it seems to be necessary to do so.

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Less commonly susceptible patients develop at low doses visual or aural complaints with cinchonism. These reactions preclude further use of quinidine inasmuch as severe complications, such as toxic amblyopia, can develop if therapy is continued.

By far the most serious complication of the central nervous system with quinidine therapy is central depression associated with respiratory arrest, convulsion, and death. It has been shown in animals that this can occur quite suddenly and at low dosage. Although sudden death in patients receiving quinidine may be due to cerebral embolism or to the development of a cardiac arrhythmia, it is likely that at least some deaths are due to sudden respiratory depression.

To reduce the incidence and severity of these allergic and idiosyncratic reactions, a quinidine test dose has long been recommended. Although the administration of a single dose of 0.2 Gm. of quinidine sulfate may be helpful, it will not detect or prevent all or even many of the reactions mentioned above. The best protection against reactions is close observation and withdrawal of quinidine when reactions occur.

Toxicity due to overdosage. The most important toxic responses to quinidine are not due to allergy or to idiosyncrasy to the drug but are rather the cardiovascular responses to overdosage.

Often the first clinically apparent effects of quinidine are electrocardiographic, that is, prominence of the U wave, Q-T prolongation, and QRS prolongation. These manifestations do not properly represent toxicity but rather therapeutic effect. Clinical experience, however, has indicated that the degree of depolarization block associated with QRS prolongation will frequently be associated with toxicity. Thus, although it is in itself not an indication for countermeasures, it should preclude a further increase in the dose.

Hypotension, on the other hand, is clearly a toxic effect. Although a depression of cardiac contractility is present at toxic levels, a reduction in peripheral resistance due to quinidine-induced vascular paralysis is the major factor causing hypotension. Direct cardiac toxicity, in addition to any depression of contractility, may be manifested by intra-atrial block, sinus depression, and sinus node exit block, simulating atrial standstill. In severe toxicity, A-V nodal block develops. In animals this is a late and irreversible sign. However, it is reversible in some patients; probably in man it occurs at a lower level of toxicity because of pre-existing disease of the A-V node.

Since quinidine is primarily a depressant, the usual clinical signs of cardiac toxicity, such as ventricular premature contractions, ventricular tachycardia, and ventricular fibrillation (rather than cardiac arrest), cannot be attributed directly to the effects of the drug on the cell membrane, but must be due to hypotension and other deleterious effects of quinidine on the cardiac muscle. Toxic levels of quinidine are associated with depression of serum sodium, serum potassium, and especially serum pH. The mechanism of these changes in quinidine intoxication is not understood, but it is likely that they contribute to the toxic manifestations.

Treatment of overdosage. There are three potential approaches to the treatment of quinidine toxicity: (1) the administration of drugs that have an opposite effect on contractility, depolarization, and repolarization; (2) the administration of drugs designed to elevate the blood pressure by increasing peripheral resistance; (3) the administration of drugs or solutions designed to correct the electrolyte abnormalities that exist.

Drugs in the first group are epinephrine, ephedrine, and isoproterenol. A decade ago it was demonstrated that epinephrine could raise the blood pressure and increase contractility in the presence of quinidine toxicity, but the effect was not striking and clinical experience was quite limited. The use of ephedrine prophylactically during the administration of quinidine has found favor in Europe on the basis of a clinical study which reported a reduction in sudden deaths when it was used. The findings of this study have not been confirmed. Isoproterenol has been shown to reverse mild cases of quinidine toxicity and to be of prophylactic value in a narrow dose range in animal studies. It has also been reported to have been successful in

the treatment of an episode of quinidine toxicity in man. Clinical experience with drugs in the treatment of quinidine intoxication in the cardiac patient is very limited; the animals in which success has been reported have usually manifested hypotension and block; it is not clear whether the ectopic beats and tachycardias seen in human toxicity would be potentiated by these drugs with any frequency.

Most of the drugs commonly used in raising the blood pressure by increasing peripheral resistance are ineffective in the presence of quinidine intoxication, apparently because of quinidine-induced paralysis of arteriolar vasoconstriction. Levarterenol, phenylephrine, and methoxamine have been shown to be ineffective in this situation. Arteriolar response to angiotensin is, on the other hand, retained to some extent, and it also favorably affects heart rate and stroke volume. Thus this pressor drug is moderately effective in quinidine-induced hypotension. Moreover, at least in animals, the effect of angiotensin has been potentiated by the simultaneous administration of disodium calcium EDTA, which has been shown empirically to improve heart rate and stroke volume. The efficacy of molar lactate in correcting the hypotension and, to a lesser extent, the arrhythmias in some cases of moderate quinidine intoxication has been apparent for several years in the laboratory and in the clinic. The earlier experiments which suggested that quinidine causes an actual depletion of intracellular sodium provided a rational basis for the molar lactate therapy, in that it was presumed that the hypertonic sodium solution drove sodium back into the cells. Since more recent studies, although supporting the concept of a delay in the transport of sodium, have failed to confirm intracellular sodium depletion, this postulated mechanism for molar lactate action can no longer be maintained. Nonetheless, there is extracellular acidosis and a lowered serum sodium, both of which the molar sodium lactate tends to correct. The recent demonstration that the organic buffer THAM has a similar favorable effect suggests that the correction of acidosis rather than the increase in sodium is the specific mechanism of action, since THAM contains no sodium. Indeed, it has been postulated that THAM is more effective than molar sodium lactate precisely because it does not increase the serum sodium and thus cause competition with calcium for membrane transfer.

Fortunately, clinically documented quinidine overdosage is quite uncommon. This has, however, prevented the accumulation of extensive clinical experience with any of the treatment routines outlined above. On the basis of the scanty information available, it would seem that the administration of a titrated amount of intravenous angiotensin and of 40 mL of molar sodium lactate or an equivalent amount of THAM with subsequent titration of buffer as needed is the best treatment of quinidine toxicity available. The role of disodium calcium EDTA and isoproterenol is less well established.

There is presently no good clinical evidence for the prophylactic use of any drug or electrolyte during the administration of quinidine.

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The effect of chlorothiazide on separate kidney function in essential hypertension

In view of recent findings that significant differences in hemodynamic behavior and electrolyte excretion exist between the two kidneys during the course of essential hypertension and the assumption that they could be responsible for the hypertensive process, a study was carried out to investigate whether these differences were modifiable by the action of a drug. Chlorothiazide was selected for this purpose.

In 10 patients with essential hypertension at rest and on a low-salt diet, normal intake of fluids, and placebo, the blood pressure was recorded daily under basal conditions until stabilized. The patients were then catheterized, each kidney 15 cm above the ureteral meatus using No. 7F and 8F catheters. Another catheter was placed in the bladder for the purpose of detecting leakage of urine. If leakage occurred, the patient was excluded from the study.

Fifteen minutes after catheterization, using standard methods, studies of renal function—glomerular filtration rate, renal plasma flow, excretion of water and sodium—were initiated.

Two 30-minute control periods were established, followed by the intravenous administration of 500 mg. of chlorothiazide, the effects of which were studied in two subsequent 30-minute periods.

Blood pressure readings were made every 5 minutes during both periods, and their average was used to calculate mean arterial blood pressure.

The percentage differences between the two kidneys were calculated by dividing the difference between them by their mean values. The result was considered to be significant only when greater than 15 per cent.

Under the action of chlorothiazide the blood pressure dropped in all patients, reaching normal values in 5.

Significant differences in glomerular filtration rate were found in 4 of the 10 patients during the control period. After administration of the drug these differences *disappeared in 3 and persisted in 1*. In 2 of the other group without differences, discrepancies appeared under the effect of the drug.

Significant differences in renal plasma flow between the two kidneys were also found in the control period in 2 patients; these differences disappeared in 1 and persisted in the other after administration of the drug. In 2 others chlorothiazide produced differences which did not exist in the control period.

Differences in the volume of urine were present in 3 patients in the control period; these disappeared in 1 and persisted in 2 under the action of the drug, whereas in 2 of those without differences, disparities appeared after administration of the drug.

Discrepancies in the concentration of urinary sodium were observed in 5 patients during the control period; these differences persisted in 2 and disappeared in 3 when chlorothiazide was administered. Differences appeared in 2 other patients, as well, under the effect of the drug.

Disparities in the excretion of sodium were present in 9 patients before the drug was given and in 8 afterward.

Differences in one or more of the functions studied during the control period were found in 9 of the 10 patients.

Glomerular filtration rate decreased under the action of chlorothiazide, but the reductions were of different magnitudes in each kidney; as a result of which discrepancies appeared or disappeared. Differences persisted in only 1 patient.

Patients with the highest blood pressure readings during the control period did not always show differences in glomerular filtration rate, nor did the extent of these discrepancies bear any relationship to the levels of blood pressure. Likewise, no correlation was found between the level of blood pressure and the differences in glomerular filtration rate as a result of the action of chlorothiazide.

Although chlorothiazide does not significantly *modify renal plasma flow, it did affect this function* unequally in the two kidneys in such a way that discrepancies either disappeared or appeared. Only in one instance did the difference encountered in the control period persist during the action of the drug. As in the case of glomerular filtration rate, discrepancies in renal plasma flow bore no relation *to variations in arterial blood pressure.*

The greatest number of disparities between the two kidneys was found in the excretion of sodium both before and after the administration of chlorothiazide. These disparities were due to differences in the concentration of urinary sodium in some patients and to differences in urinary volume in others. However, in 3 patients the differences could not be

attributed to either of these two factors. These results seem to suggest that the statistical method used has limitations when applied to derived data, such as sodium excretion (U V), since insignificant differences in each factor when varying in the same direction may become significant when multiplied.

The number of patients with differences in the excretion of sodium was greater than the number with disparities in glomerular filtration rate, and, hence, in sodium load. This indicates that the discrepancies in sodium excretion were due mainly to a tubular disorder.

Study of the effect of chlorothiazide upon the functional differences between the two kidneys in essential hypertension indicates that under the action of this drug these discrepancies may either disappear or appear except for the differences in sodium excretion, which tend to persist in spite of the fact that the range of sodium excretion is different before and during the effect of the drug.

The persistence of differences in the excretion of sodium indicates its importance in essential hypertension. However, it does not establish whether these differences are related to the genesis of this process or are a consequence of it.

The conclusions are: (1) that functional differences between the kidneys in essential hypertension have no relationship to levels of arterial blood pressure; (2) that under the action of chlorothiazide, disparities between the kidneys may disappear or appear indicating that they are functional in nature; (3) that the difference between the two kidneys in the excretion of sodium is one of the most frequent discrepancies in essential hypertension. This difference may be attributed to a tubular functional inequality that persists during the action of chlorothiazide.

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Endogenous creatinine clearance and the glomerular filtration rate

In clinical medicine we are beset by two conflicting interests—the need for accurate knowledge of vital bodily functions and the practical difficulties of making such measurements in patients. The glomerular filtration rate is one such vital function, and various methods of measuring it have been devised only to be dropped in routine clinical investigation because of their tediousness and technical difficulty. Thus, thiosulphate clearance[1] and inulin clearance[2] are rarely used in the clinical work-up of a hospital patient because of their requirement of constant intravenous infusion techniques and the desirability of a urethral catheter to obtain accurately timed collections of urine. Nevertheless, in clinical research, inulin, thiosulphate, and, more recently, radioactive vitamin B_{12}[3] are in routine use for measurement of the glomerular filtration rate. The search for convenient clinical methods for measuring the glomerular filtration rate, without the need for infusions of substances, has been centered on two substances—urea and creatinine. It was soon shown that urea clearance was less than inulin clearance and that the ratio of insulin to urea clearance was dependent on the flow of urine. When creatinine clearance was investigated, it was found that exogenous loading with creatinine was necessary in various mammals in order to obtain adequate plasma creatinine levels, and in the cat the exogenous creatinine clearance was closely related to the glomerular filtration rate. In the dog the findings were controversial.[4] In the rat,[5] anthropoid apes,[6] and man,[7] exogenous creatinine clearance was greater than the glomerular filtration rate, i.e., creatinine was secreted. Exogenous creatinine clearance could be lowered to that of the glomerular filtration rate by blocking creatinine secretion[8] by Diodrast, caronamide, and PAH.[9] Endogenous creatinine has a plasma level in man which is high enough to measure, and various workers then estimated the value of endogenous creatinine clearance in man,[10] but the Jaffé reaction, generally used, was found to estimate both creatinine and "noncreatinine" chromogen unless steps were taken to estimate only the true creatinine by

absorption on Fuller's earth (Lloyd reagent). Using these techniques of true creatinine clearance some authors found that in normal people the ratios of endogenous creatinine clearance to inulin clearance[1-20] were 1 whereas other authors found that the use of creatinine-specific microbiologic techniques[21] gave ratios of less than 1 in normal people. Miller and his colleagues[21] using this method found that in patients with proteinuria the true endogenous creatinine clearance was greater than the glomerular filtration rate as measured by inulin. In infancy congestive heart failure oliguria[22] and severe hypoxia,[23] the ratios of endogenous creatinine clearance to inulin clearance was less than 1. Other authors have also found endogenous creatinine clearance to be of little use in measuring glomerular *filtration rate because of its dependence on the* rate of flow of urine.[24-26] Nevertheless, in the English literature, endogenous creatinine clearance continues to be used by nephrologists as a clinical measurement of the glomerular filtration rate.[27,28] Recently the controversy has been reopened, with one group[29] demonstrating the frequent secretion of endogenous creatinine in 5 out of 6 patients with proteinuric states finding ratios of endogenous creatinine clearance to inulin clearance of up to 2.37 and suggesting that the ratio was unpredictable from case to case. They advised that endogenous creatinine clearance be no longer used in cases in which an accurate measure of the glomerular filtration rate is needed. Their results received support from others.[30]

Recently another group of authors[31] found that endogenous creatinine clearance was still useful as a measure of glomerular filtration rate if the value was above 90 ml. per minute. As the inulin clearance fell, the ratio of creatinine clearance to inulin clearance rose progressively to over 1.5 when the inulin clearance was below 20 ml. per minute.

The use of plasma concentration of endogenous creatinine as a rough clinical measure of glomerular filtration rate has been advocated by two groups of German workers,[32,33] but although there is a statistical correlation between inulin clearance and plasma creatinine, the latter is only as useful an index of renal function as is the blood urea level if the patient is taking a normal diet.

It may be concluded that endogenous creatinine clearance will provide a rough estimate of renal function but that in all precise clinical investigation, in spite of the convenience of endogenous creatinine clearance, it is not an accurate measure of the glomerular filtration rate and should be discarded.

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Effects of reducing agents on indocyanine green dye*

The development of indocyanine green dye (ICG) as an indicator for dye-dilution techniques in 1956 has been followed by enthusiastic acceptance of this material by persons who utilize indicator-dilution methods for circulatory studies. Today, in all likelihood, ICG is the most commonly used indicator for such studies. A major advantage of ICG which accounts for much of its popularity and usefulness is that it is rapidly excreted by the liver in a matter of minutes and can therefore be used repeatedly. It does not produce tissue staining after intravascular injection, and in so far as is known, no toxic effects have been recognized in human beings. Since the peak absorption of ICG (800 mμ) approximates the isobestic point of reduced oxyhemoglobin, fluctuations in oxygen saturation of blood have little effect on the optical density of ICG in whole blood.

However, ICG is not an "ideal" substance for use in indicator-dilution techniques. It is poorly soluble in saline solutions, deteriorates with time after it is in aqueous solution, and in whole blood does not rigidly follow Beer's law. Densitometry of whole blood at 800 mμ is subject to some nonspecific variations, including variations in carbon dioxide tension and hemoglobin concentration. In spite of these "imperfections," ICG in application is a highly satisfactory and safe material for most diagnostic and investigative purposes.

We have recently encountered a problem with ICG which is not generally appreciated and which is potentially significant. After some concern over apparent discrepancies in determinations of cardiac output, it was discovered that a preparation of heparin (Lipo-Hepin) used as an anticoagulant, regularly reduced the optical density of ICG in blood and in plasma. This particular preparation of heparin contains 0.1 per cent sodium bisulfite and 1 per cent benzyl alcohol as preservatives. Subsequent observations showed that sodium bisulfite per se was markedly effective in altering the spectrophotometric characteristics of ICG in plasma and in water. Sodium bisulfite in a concentration of 0.0015 per cent lowered the optical density (800 mμ) of ICG (1 mg. per liter of plasma) by an average of 72 per cent. This effect began immediately and was maximal in less than a minute. Interestingly, the deterioration of ICG by Lipo-Hepin was much greater in plasma than in aqueous solutions. Wetting the barrel and filling the dead space of a 50-ml. syringe with the above-mentioned heparin preparation reduced the densitometric estimation of ICG concentration by 15 to 20 per cent during calibration of dye in blood. Such errors would of course be directly carried over to any calculations of blood flow. Twelve of the heparin preparations listed in a recent issue of the *Medical Letter*[1] were tested for their effect on ICG; only the Riker preparation had sodium bisulfite as a preservative, and it was the sole heparin preparation that showed an effect on ICG. The other preparations had as preservatives benzyl alcohol, propylparaben, methylparaben, chlorobutanol, and phenol.

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[1] See Med. Letter ... Northridge, Calif.

It is not surprising that sodium bisulfite should have such an effect on ICG since the spectral characteristics of other cyanine dyes are subject to the action of reducing agents. We have found that sodium metabisulfite, sodium borohydride, and potassium borohydride also markedly lower the optical density of ICG at 800 mμ. Undoubtedly other reducing agents would produce similar changes in the optical density of ICG; fortunately opportunities for contamination of ICG by such agents are probably rare. Persons using heparin as an anticoagulant for ICG studies should be sure that the preparations are free from sodium bisulfite or similar reducing agents.

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The WPW syndrome in cattle

The WPW syndrome in cattle has been described by Van Arsdel and Bogart.[1] The ECG tracings exhibited a shortened P-R interval, changed QRS pathways, lengthened QRS interval, and the characteristic delta wave considered to be diagnostic of the WPW syndrome.

Normally, the P-R interval can be expressed as a linear function of the cycle length. In the described condition in cattle, the curtailed P-R (conduction bypass or accelerated conduction) exhibits a P-R interval which remains constant over a wide range of cycle lengths. The increased QRS interval of the WPW syndrome also exhibits constancy. It thus becomes apparent that the widening of the QRS interval during a WPW episode does not exactly compensate for the shortening of the P-R interval, except for a small area of the graphed data. It is suggested that the data obtained from recumbent human subjects fall within this small area of exact compensation.

In a three-dimensional projection, the orientation of the P-wave vector is similar whether WPW or normal. The QRS and T-wave vectors change markedly in the shift from normal to WPW configurations, but maintain approximately the same QRS-T angle. This QRS-T angle is maintained in spite of the marked directional changes in axes involved, and may reflect basic physiologic principles.

The magnitude of the QRS vector greatly increases during a WPW episode. Changes in the T-wave potential are less obvious.

Illustrations include the ECG tracings, charts, graphs, tables, and vector loops to substantiate the diagnosis.

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Editorial

Current status of steroid therapy in rheumatic fever

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During the past 15 years steroids have been widely used in the treatment of rheumatic fever. The voluminous literature on this subject is contradictory and the advantages and limitations of these drugs have not been clearly defined.

The basic research to assess the value of steroids in the treatment of rheumatic fever was undertaken in a cooperative clinical trial conducted jointly by the American Heart Association and the Medical Research Council of Great Britain. To determine whether these new drugs represented a significant advance, ACTH and cortisone were compared with aspirin because salicylate therapy had been standard treatment for rheumatic fever for 75 years. This study, based on 497 children, was designed to answer the following questions: (1) What is the relative effectiveness of these three agents in altering the course of the acute disease or in suppressing its clinical manifestations? (2) What is the relative effectiveness of these three agents in preventing rheumatic heart disease?

The U.K.-U.S. Joint Report reached the following conclusions: (1) No evidence was obtained to indicate that ACTH, cortisone, or aspirin uniformly terminated the active rheumatic process. (2) Steroid therapy resulted in prompt subsidence of certain acute manifestations, but they tended to reappear after cessation of treatment. (3) After 1 year the incidence of residual rheumatic heart disease was essentially the same in patients treated with steroids as in those treated with aspirin.

After a follow-up period of 5 years the findings showed no significant difference from those recorded at the end of 1 year. Furthermore, an analysis of the data showed that, irrespective of the therapy employed, the incidence of residual rheumatic heart disease correlated directly with the degree of cardiac involvement present at the time that treatment was instituted.

The U.K.-U.S. reports (1955 and 1960[2]) represented a model of how clinical trials in a disease as variable as rheumatic fever should be conducted. To prove the superiority of any therapeutic regimen the following requirements are essential: (1) The drugs must be administered *concurrently* on a blind and random basis. (2) The cardiac status of the patients at the time at which therapy is instituted must be accurately defined. (3) Only patients with moderate to severe clinical carditis should be included in the study, because patients with minimal cardiac involvement usually recover completely, irrespective of the

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therapy employed (4) The severity of the carditis must be comparable in the various treatment groups.

The effect of steroid therapy on the acute manifestations of rheumatic fever is well known Fever and arthritis respond dramatically Furthermore most observers agree that in patients with severe acute myocarditis, especially if accompanied by congestive failure the immediate response is usually more rapid with steroids than with aspirin The critically ill toxic child *tolerates steroids better than aspirin and* a feeling of well being is induced The *aspect of steroid* therapy which has remained contraversial is whether these *drugs, despite their marked effect on the* acute symptoms, really reduce the incidence of residual *rheumatic heart disease.*

The dosage of ACTH and cortisone employed in the U K U.S Joint Report were relatively small and were administered for only 6 weeks. Several observers thought that the failure to reduce the incidence of residual rheumatic heart disease might have been due to inadequate steroid dosage.

In a series of *uncontrolled* studies a low incidence of residual rheumatic heart disease was reported by several observers in patients treated with large *doses of steroids* for 10 to 12 weeks.[5-7]

In two controlled studies the value of large doses of steroids given for 12 weeks was investigated The Combined Rheumatic Fever Study Group (1960)[8] reported that the incidence of residual rheumatic heart disease in patients with moderate to severe carditis was essentially the same as in a comparable group treated with aspirin for the same length of time. On the other hand Dorfman and associates (1961)[9] in a similar study reported less heart disease in patients given *steroids* than in those treated with aspirin However *these findings are open to question* because the criteria for the diagnosis of clinical carditis were not rigid and children with mild carditis were included in the study

Wilson and her co-workers,[10-14] in a series of *uncontrolled* studies, have consistently claimed that prednisone in very large doses given for 1 to 2 weeks prevents residual *rheumatic heart disease* in 96 per cent of patients so treated

In a second study the Combined Rheumatic Fever Study Group (1965)[15] *tried* unsuccessfully to confirm these findings. The incidence of residual rheumatic heart disease was essentially the same in patients with moderate to severe carditis given short term intensive prednisone therapy for 1 or 2 weeks as in a comparable *concurrent* group of children treated with conventional doses of aspirin for 8 weeks.

Summary

*There is no specific therapy for the treat*ment of rheumatic fever Two effective *suppressive drugs are available* salicylates and steroids. Both are palliative and not *curative Neither of these agents shortens* the course of the disease There is no definite evidence that *either* salicylates *or* steroids given early or late in high or low dosage for long or short periods uniformly terminate the activity of the rheumatic process or prevent cardiac damage

Both salicylates and steroids are effective anti inflammatory agents for controlling the exudative manifestations of rheumatic fever Steroids are more potent than salicylates and usually produce *a more rapid* subsidence of the acute manifestations. In patients with severe *carditis in whom the* inflammatory edema in the myocardium *may be life threatening* steroids should be employed until the acute symptoms abate followed by a course of salicylates continued for several weeks.

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Clinical communications

Nonspecific and beta adrenergic blocking effects of Alderlin in angina pectoris

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A new beta-adrenergic blocking compound designated as Nethalide in England and Alderlin in the United States, which lacks sympathomimetic effects, slows heart rate[1] and blocks mobilization of free fatty acids.[2] Although it is said to alleviate angina pectoris and myocardial ischemia,[3] the vagaries of circumstances affecting the syndrome of angina pectoris make appraisal of symptomatic drug therapy difficult. In considering further investigation, it was hypothesized that a beta blockade should protect the myocardium from adrenergic stimulation which wastes oxygen and should improve exercise capacity in patients with angina pectoris. The possibility of objective evaluation is afforded by those patients who transiently exhibit segmental S-T depression on the electrocardiogram in response to the stress of exercise.

The experimental design for this clinical investigation involved four procedures: (1) selection of patients with typical angina pectoris who exhibited myocardial ischemia (segmental S-T depression) upon testing of exercise capacity but who were not being treated with digitalis; (2) demonstration of greater capacity when retested after intravenous therapy with Alderlin; (3) double-blind evaluation of oral therapy with Alderlin and a placebo; (4) determination of therapeutic blocking of myocardial chronotropic response to isoproterenol intravenously.

Material and methods

Medical records of over 100 patients were reviewed to select patients with a history of repeated attacks of angina pectoris with exercise who were usually relieved by rest and/or nitroglycerin sublingually. Fourteen patients, 13 men and 1 woman, with an average age of 57.4 years were selected. Each showed segmental S-T ischemia transiently on a precordial lead electrocardiogram immediately after maximally tolerated exertion. None had other complicating diseases or evidence of recent infarction by history and by 12 lead electrocardiogram at rest.

Capacity for exercise was tested by continuous exertion on a treadmill, where the speed and grade of walking was increased every 3 minutes as follows: *first stage*—1.7 m.p.h., 10 per cent grade; *second stage*—2.5 m.p.h., 12 per cent grade; *third stage*—3.4 m.p.h., 14 per cent grade; *fourth stage*—4.2 m.p.h., 16 per cent grade. Exercise was terminated when the patients were physically unable to continue exertion because of the severity of chest pain, dyspnea, fatigue, or other symptoms. Unless the electrocardio-

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gram (which was monitored throughout) exhibited paroxysmal ventricular tachycardia, exertion was not stopped because of ischemic changes or isolated premature beats. This test verified therefore the reproducibility of the anginal syndrome, and it defined capacity for exertion and severity of myocardial ischemia with effort.

After the initial exercise test, 50 mg of Alderlin were injected intravenously; the patient was observed for 20 to 30 minutes for any untoward effects, and then the same exercise test was repeated. Any changes in performance were evaluated in terms of duration of exercise, symptoms, and ECG responses.

A double-blind evaluation of oral Alderlin therapy was initiated by instructing the hospital pharmacist to supply each patient with enough tablets for 1 week of either Alderlin (100 mg.) or a physically indistinguishable placebo which had been selected on a random basis. The patients were given instructions to take the tablets as follows: *First day*—One tablet at breakfast, lunch, dinner, and bedtime, or a total of four tablets. *Second day*—One tablet at breakfast, two tablets at lunch, one tablet at dinner, and two tablets at bedtime, or a total of six tablets. *Third day (and thereafter)*—Two tablets at breakfast, lunch, dinner, and bedtime, or a total of eight tablets. In addition, the patients were given a record sheet on which to record the number of tablets taken, the number of nitroglycerin tablets consumed, together with symptoms, heart rate, and any untoward effects.

These patients were seen each week for 4 consecutive weeks. The interim clinical history was reviewed in regard to exercise symptoms, and consumption of nitroglycerin, and the exercise capacity test was performed again. Eleven patients (Group A) were seen on each visit by the same investigator (G.B.S.), who recorded a clinical impression of whether the medication was placebo or Alderlin. Then each patient was tested with an intravenous infusion of isoproterenol (0.2 mg. in 500 ml. of 5 per cent dextrose in water administered at a rate of 2 to 5 μg per kilogram of body weight per minute). Failure of this infusion to increase heart rate or to initiate ventricular premature beats within 5 minutes indicated an effective blockade of circulating catecholamines. At the end of 4 weeks a general statement was made by each participant concerning his own assessment of the therapeutic value of the drug.

Eleven men (Group A) were followed through the entire study and were clinically evaluated each week by the principal investigator. The last 3 patients (Group B) were evaluated and followed each week by various cardiology residents.

Results

I. Intravenous Alderlin. After intravenous injection of 50 mg. of Alderlin average

Table I. Circulatory responses to exercise

	Initial control	*After intravenous Alderlin*	*After oral placebo*	*After oral Alderlin**
Heart rate				
First stage	117 ± 20	104 ± 18	103 ± 8	95 ± 7
Second stage	125 ± 19	118 ± 15	123 ± 7	109 ± 8
Third stage	——	136 ± 26‡	141 ± 9	117 ± 5
Maximal	134 ± 19	128 ± 20	136 ± 11	116 ± 11†
Blood pressure after exercise	143 ± 18 82 ± 8	137 ± 11 84 ± 9	147 ± 10 82 ± 10	135 ± 9 78 ± 9
Duration of exercise (sec.)	297 ± 193	358 ± 158	468 ± 67	447 ± 76

*Paired observations in patients who received both placebo and blocking compound.
†p < .05.
‡[illegible]

heart rate promptly slowed from 87 to 70 per minute. Orthostatic dizziness and/or lightheadedness were experienced by most of the 14 patients transiently. Tinnitus was noted by one. Since intravenous infusion of isoproterenol failed to increase heart rate in all instances, an effective beta-adrenergic blockade had been established.

Whereas initially chest pain always terminated the exercise test, after intravenous Alderlin 5 patients stopped exertion because of dyspnea, fatigue, and claudication in the legs. Although heart rates were lower for each stage of exercise and for maximal exertion (Table I), none of these changes were significant. The average duration of exercise increased from 297 to 358 seconds, or nearly to the end of the second stage at 2.5 m.p.h. and 12 per cent grade. Three patients, however, were able to complete the third stage of walking at 3.4 m.p.h. and 14 per cent grade, and 2 entered the fourth

Table II. Relationship of clinical assessment of double-blind oral therapy to actual therapy in 14 patients

Patients	Weeks of observation				Accuracy of assessment
	First	Second	Third	Fourth	(Total)
Group A (Initial)					
1. B.P.	A* A†	P P	–	–	2/2
2. L.H.	A A	P P	–	–	2/2
3. H.M.	A A	P P	P A	A A	3/4
4. W.H.	P P	A A	P P	A A	4/4
5. J.W.	P A	P P	P P	P A	2/4
6. W.B.	P P	A P	A P	A A	2/4
7. D.R.	A A	A A	P P	P A	3/4
8. H.C.	A A	P P	A P	A A	3/4
9. J.S.	A A	P P	–	–	2/2
10. E.F.	P P	A A	P P	–	3/3
11. C.D.	P P	A A	P P	A P	3/4
					29/37 Subtotal
Group B					
12. R.L.	A P	P P	A P	A P	1/4
13. D.C.	P P	A A	P P	A A	4/4
14. R.M.	A A	A A	A A	A A	4/4
					9/12 Subtotal
					38/49 Total

*Predicted therapy as determined by clinical examination.
†Actual therapy as recorded by pharmacy.
A, Alderlin. P, Placebo.

stage of walking at 4.2 m.p.h. and 16 per cent grade.

II. Oral Alderlin. At the end of each of 4 consecutive weeks during which the patient had been taking either an oral placebo or Alderlin, they were re-evaluated for any changes in symptoms, exercise tolerance, consumption of nitroglycerin, and exercise capacity (Table II). In 38 of 49 clinical appraisals (77 per cent, $p < .001$) the decisions of whether patients had been treated with either Alderlin or placebo were correct when the records in the pharmacy were examined. A very careful review of the interim activities, symptoms, and subjective feelings of the patient, as well as heart rates at rest and during exercise, proved to be the most useful criteria for this evaluation. Even though a form was provided for recording the number of nitroglycerin tablets consumed, only a few patients made an accurate tally. Therefore, this was not useful for assessing either the severity or frequency of angina. Other symptoms reported during the oral medication were those of orthostatic hypotension and gastrointestinal irritation. One patient noted tinnitus on two occasions. This subsided promptly when the dosage was reduced to 500 mg. per day. A mild skin rash was noted in one man who was exposed to allergens; another complained of moderately severe diarrhea.

Since oral Alderlin prevented any increase in heart rate from intravenous isoproterenol in every instance, an effective beta-adrenergic blockade had been achieved by the quantity of drug prescribed.

Although heart rates at rest were slightly lower after a week of oral Alderlin therapy

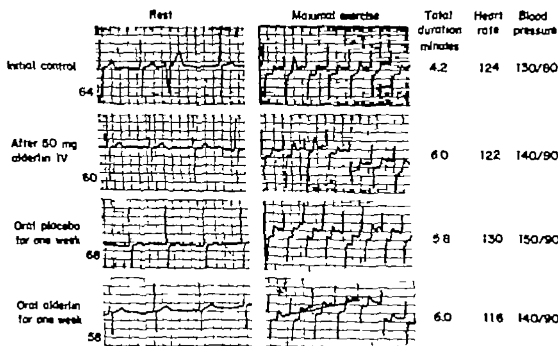


Fig. 1. Precordial electrocardiograms recorded from left precordial lead at the V5 position at rest and during maximal exertion in E.H., a 69-year-old man with typical angina pectoris. Note the occasional premature ventricular beats in the initial control tracings, and the significant depression of the S-T segment on four separate exercise tests. Heart rate, both at rest and at maximally tolerated exertion, was slower with either intravenous or oral Alderlin therapy, whereas blood pressure responses were variable. Although duration of exertion was greater after intravenous therapy, no further increments occurred with oral therapy, despite the slower rate. The magnitude of the segmental S-T depression was not altered by therapy. He was not taking digitalis during these observations. Finally, the maximal heart rates are unusually low for age, but not for diagnosis of angina pectoris, as previously reported elsewhere.

and they were also lower at every comparable level of exercise only the moderate reduction in maximal heart rate was significant ($p < .05$) (Table I) Blood pressure ventilation and intakes of oxygen failed to demonstrate *any significant differences*. None of the electrocardiograms showed any change in S-T depression at rest during maximum exercise or in recovery whether the patient was on placebo or Alderlin therapy (Fig 1) This disparity indicated the opportunity for subjective observer patient bias to occur

Whereas average duration of maximal exertion during placebo therapy was prolonged 2 5 minutes beyond the initial control test of exercise oral therapy with Alderlin did not improve exercise performance (Table I) Indeed mean duration with placebo therapy was negligibly greater than with oral Alderlin (468 to 448 seconds) It was of interest however that each week the duration improved progressively in some patients, whereas in others it remained unchanged regardless of the type of medication Inquiry revealed that this program had increased physical activities in many cases One individual improved exercise tolerance for walking from 4 blocks to 4 miles per day but he was still limited at that time by chest pain and fatigue This steady increase in exercise tolerance indicated nonspecific benefits from reassurance as a result of frequent testing and increasing familiarity with the testing procedure as well as physical conditioning Alternatively it might represent increasing collateral circulation and diminishing myocardial ischemia but serial electrocardiograms failed to indicate this possibility

Symptoms which limited exercise on the treadmill after oral therapy were very similar to those observed during the initial test They consisted of angina and in some cases dyspnea and claudication Only 2 patients noted less chest pain with exercise when taking oral Alderlin

When interviewed after the termination of Alderlin therapy 11 of 14 patients were convinced of having benefited from it, and were interested in prolonged therapy

Discussion

Although the pain of angina pectoris is typically relieved by rest and/or the use of nitroglycerin sublingually clinical experience reveals rather marked fluctuations in the promptness and degree of symptomatic relief Numerous factors other than vascular disease may contribute to acute myocardial ischemia such as increased ventricular work from acceleration of heart rate or augmentation of stroke work with increments in pressure and volume of blood ejected per beat Myocardial metabolism is enhanced by sympathetic and catecholamine stimulation Inasmuch as the myocardium is supplied by catechols a chemical blockade to prevent excessive myocardial metabolism might conceivably make the available coronary circulation sufficient for the needs.

Experimental studies of Alderlin demonstrate rapid jejunal absorption selective localization in many tissues, except liver and adipose cells and rapid metabolism in the liver[1] Alderlin regularly slows heart rate and the speed of myocardial contraction with rapid intravenous injection the blood pressure may fall from myocardial depression The drug effectively blocks responses to injected epinephrine or isoproterenol and larger doses of it reduce responses to sympathetic stimulation In clinical studies, Dornhorst and Robinson[3] observed bradycardia especially with low levels of exercise and failure of blood flow in the forearm to increase with isoproterenol Heart rates were lowered in patients with ischemic heart disease exercise tolerance was increased and electrocardiographic evidence of myocardial ischemia with exertion was diminished Pilkington and associates[2] found that this compound prevented the mobilization of free fatty acids by epinephrine More recently Chamberlain and Howard[4] studied the responses of 10 normal medical students to the exercise of walking at 2 5 m p.h and 7 degree incline on a treadmill and found that this compound had little effect on cardiac output. Heart rates were lower and pulse pressures were diminished in response to the same amount of exercise after the drug There was little change in the mean pressure or resistance Although the stroke volume may have been increased the prolonged systolic ejection time lower pulse pressure and slower heart rate did not indicate that ventricular work was maintained at the

same level. These observations also revealed the minor importance of sympathetic and/or catecholamine influences in increasing cardiac output with exercise. Apthorp, Chamberlain and Hayward[6] studied exercise responses to walking on a treadmill in 8 patients before and after bilateral upper thoracic sympathectomy. Effort tolerance was increased twofold to threefold in 6 patients, and there was a delay or abolition of ischemic abnormalities in the electrocardiogram during exertion. In 6 patients who were also studied again after use of the beta-sympathetic blocking compound, effort tolerance was increased 50 per cent in 3 of them. The authors postulated that reduction in sympathetic drive increases myocardial efficiency, since less ventricular work is performed for the same coronary arterial supply of oxygen. They also noted a paradoxical effect in heart failure, since patients with incipient left ventricular failure developed more angina and dyspnea with exertion when under treatment with this drug. The principal benefits of this compound in ischemic heart disease are therefore conservation of myocardial oxygen consumption due to prevention of excessive tachycardia and rapid systolic contraction. Whenever the oxygen supply is impaired by coronary occlusive disease this effect is beneficial, provided that stroke output is not critically impaired and left ventricular failure does not ensue.

In this study, all 14 patients showed a capacity for more prolonged exercise after Alderlin had been administered intravenously. Clinically, it was effective in 29 out of 37 double blind weekly appraisals of oral therapy when evaluated carefully by the same observer (G.B.S.). Indeed 11 patients wanted to continue treatment with it. Although heart rates at rest and during exercise were lowered, and the duration of exertion and capacity for maximal effort were increased in 3, the average responses for the entire group of patients were not improved objectively. Furthermore, myocardial ischemia was just as evident at maximally tolerated exertion, as judged by the segmental S-T depression of the electrocardiogram. Possibly, the oral dosage was not quite optimal, yet it was clearly sufficient to block responses to intravenous isoproterenol in every instance and some patients noted minor untoward effects. Nevertheless the inability to prolong the mean duration of maximal exercise suggested that some of the patients may have more closely approached left ventricular failure.

This disparity with other studies which reported a reduction in, or disappearance of myocardial ischemia in the exercise electrocardiogram[4] remains unresolved. Whether some of the patients reported by others were studied too soon after myocardial infarction and possibly were still undergoing evolutionary changes in collateral arterial circulation is not readily apparent. Now that Alderlin has been replaced by a more potent compound, further observations will be needed to determine the ultimate therapeutic role of beta-adrenergic blockers in the management of angina pectoris.

Summary and conclusion

1. Preliminary intravenous therapy with a new beta adrenergic blocker, Alderlin, has been compared with double-blind oral therapy in 14 patients with angina pectoris.

2. Although heart rate tended to be slower, only maximal heart rate during oral Alderlin therapy showed a significant reduction. Yet an effective beta-adrenergic blockade was demonstrated by the failure of intravenous isoproterenol to increase heart rate during either intravenous or oral therapy with Alderlin.

3. Evidence of myocardial ischemia with maximal exertion, as manifested by segmental S-T depression in the precordial electrocardiogram, was not altered by Alderlin therapy.

4. Clinical symptoms and exercise capacity progressively improved and 2 patients observed a decrease in the severity of angina pectoris. Since these effects occurred with either oral Alderlin or placebo therapy, the responses were probably nonspecific effects of medical investigation and supervision.

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The prognosis of complete left bundle branch block

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In 1951 Johnson, Messer, Shreenivas, and White[1] published the results of their study of 555 patients with left bundle branch block which had been discovered between 1937 and 1948 at the Massachusetts General Hospital. The average survival time of these patients, including those still living at the time the study was completed, was 3.3 years. Several other observations were made on this group of patients, including the following: (1) The condition is more common in males than in females, and the prognosis is somewhat better in females. (2) Nearly 90 per cent of the patients were over 50 years of age. (3) In general, the patients with the longest QRS durations had the shortest survivals. (4) ECG evidence of left bundle branch block indicates heart disease. Although the average survival time was only 3.3 years, a long survival time free of symptoms was not incompatible with left bundle branch block. The prognosis depends upon associated findings and the underlying heart disease.

The present study was undertaken out of curiosity as to whether the prognosis of left bundle branch block had changed in the past 15 years, since there has been considerable improvement in the methods of treatment of cardiac disease during this interval.

Study method

The study was carried out at the University of Kansas Medical Center and the Kansas City Veterans Administration Hospital. At these institutions, electrocardiograms are cross-indexed according to diagnosis when they are interpreted. All eleccardiograms indexed as showing a complete left bundle branch block during the years 1954 to 1963 were obtained. The criteria followed for accepting the diagnosis of complete left bundle branch block were those established by the New York Heart Association.[2] Those electrocardiograms in which the diagnosis was in any way questionable were eliminated. This left a group of 164 patients. The clinical records of these patients were obtained and an attempt to trace the patients was made. Only those patients whose present status could be determined were kept in the study. If the patient had died, the date of death was ascertained. If the patient was still alive at the time the study was completed, this fact was established with certainty. A final group of 146 patients remained after these criteria had been met. For the purpose of this study the date of the first diagnosis of left bundle branch block was taken as the first time this diagnosis was made by electrocardiogram in these hospitals.

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Results

Table I divides the group according to sex and age at the time of diagnosis. The inclusion of patients from the Veterans Administration Hospital assured the predominance of males. In considering the age distribution it must also be taken into account that veterans are not representative of the general population as to age. Veterans ages generally fall into two clusters determined by the two World Wars. It can be seen from the table however that the large majority of the patients were over the age of 50.

Table II divides the patients according to sex and shows how many were alive or dead at the time the study was completed.

The duration of survival from the time of diagnosis of complete left bundle branch block for the entire group averages 36.0 months. This includes the patients who were still living at the time the study was

Table I. Age at the diagnosis of complete left bundle branch block

	Under 40	40-49	50-59	60-69	70-79	80 and over	Total
Male	5	2	19	36	28	8	98
Female	3	4	5	9	16	11	48
Total	8	6	24	45	44	19	146

Table II. Survival at the completion of the study

	Alive	Dead	Total
Male	38	60	98
Female	21	27	48
Total	59	87	146

Table III. Duration of survival of patients who were dead at the completion of the study

	Years										Total
	<1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	
Number of patients	27	18	21	9	1	2	3	1	2	2	86

Table IV. Duration of survival of patients who were living at the completion of the study

	Years										Total
	<1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	
Number of patients	3	10	10	3	3	11	5	8	1	6	60

Table V. Etiology of the underlying heart disease

Etiology	Male	Female	Total
Arteriosclerosis	70	29	99
Hypertension	11	8	19
Rheumatic fever	4	2	6
Syphilis	1	1	2
Coarctation of the aorta		1	1
Ventricular septal defect	1		1
Patent ductus arteriosus	1		1
No apparent cardiovascular disease	10	7	17
Total			146

completed. This figure was 40.1 months for females and 34.5 months for males.

In Table III the patients who have died are divided according to duration of survival from the time the diagnosis of left bundle branch block was made. In the same manner, Table IV shows the duration of survival of the patients who were still alive at the time the study was completed.

Table V lists the etiologies of the underlying heart disease in this series of patients and indicates the frequency with which each occurred.

Discussion

We were surprised to find that in our cases the average duration of survival after the diagnosis of complete left bundle branch block was actually a few months shorter than that reported in the previously mentioned study done 15 years ago. Although no effort was made to match these two studies in terms of the populations studied or methods of case selection, it was expected that the average duration of survival would be longer in the more recent study because of recent advances in the treatment of heart disease.

Although it seems to be clear that complete bundle branch block is in general a poor prognostic sign, it has been emphasized that in any individual case the prognosis is determined by the severity of the underlying heart disease and is not influenced by the disturbance in conduction.[1,3] Complete left bundle branch block is apparently always due to underlying organic heart disease, but in some individuals the cardiac involvement aside from the block may be minimal so that these people may have a prolonged survival with normal physical activity.[1,4]

Summary

In a study of 146 patients with complete left bundle branch block the average duration of survival after the conduction disturbance had been diagnosed was 36 months.

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A simplified method of recording the jugular venous pulse

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A method of revealing jugular venous pulsations using a thin cardboard indicator taped to the neck (Fig. 1) has been described in a previous paper.[1] Its purpose is to amplify and thereby make apparent to one or more observers subtle pulsations which under poor lighting conditions might otherwise be difficult to demonstrate. I have recently learned that a similar device has been used in Europe as an aid not in clinical inspection but in recording the venous pulse by a photoelectric technique.[2]

The European method described by Altmann requires a combined photocell and light source apparatus, the beam of which is interrupted by the pulse waves transmitted to the paper indicator. A multiple channel recording instrument traces the jugular venous pulse, electrocardiogram, and phonocardiogram simultaneously. The obvious advantage of such a system is that the pulsations are not influenced by the recording instrument, as may occur with the transducer methods usually employed in this country. The major disadvantage of the method as described is the need for complex and expensive equipment, in effect restricting its use to research laboratories.

The purpose of this paper is to describe a simplified and quite inexpensive modification of the photoelectric recording method making use of a standard electrocardiograph plus equipment which can be purchased for less than $2.00.

Method

A selenium photocell with an output of $\frac{1}{4}$ to 0.4 volts and $1\frac{1}{4}$ to 2 milliamps in sunlight (Fig. 2) is mounted in a window cut in the bottom of a match box and connected by alligator clips to the terminals of any bipolar electrocardiographic lead. The sliding cover of the match box varies the amount of light impinging on the cell (Fig. 3). The sensitivity of the cell is such that no extra light source is required if the neck region is reasonably well illuminated.

The patient is placed in that position which imparts maximal pulsations to the paper indicator; the position varies from supine to upright in accord with the level of venous pressure. The right side of the neck is used routinely, since there is normally a more direct anatomic communication between the right atrium and superior vena cava and the right innominate and internal jugular veins. The location of the indicator depends on whether pulsations are more prominent in the external or internal jugular vein. In the latter case the supraclavicular fossa or the area of the neck just below the angle of the jaw are usually best. The photocell unit is positioned $\frac{1}{4}$ to $\frac{1}{2}$ inch from the tip of the indicator, which by its

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movement alters the intensity of light falling on the cell thus recording the pulse waves. When the leads are connected to both the patient and the photocell in series a composite tracing is recorded the R waves of the electrocardiogram permitting timing of the a, c, and v waves of the venous pulse (Fig 4)

Discussion

Although the practical value of observing the jugular pulse at the bedside has largely been overshadowed by the development of the electrocardiograph much of the information contained in a "rhythm strip" for example can be gained by inspection of the neck. Using the polygraph an instrument which recorded venous and arterial pulses simultaneously MacKenzie was able in the early part of the century to analyze various arrhythmias, and in fact was the first to discover the absence of atrial systole in "perpetual irregularity of the heart" (atrial fibrillation)[3,4] Although it is certainly true that electrocardiography has advanced the study of functional and structural heart disease to a degree previously unheard of the fact remains that by observation of the neck veins certain conclusions can be reached with certainty which can only be assumed by the electrocardiographer One may guess that there is a P wave buried in a given QRS complex but there can be no doubt when cannon waves are seen in the jugular pulse since they occur only when the right atrium contracts against a closed tricuspid valve. Thus noting the presence and degree of regularity of cannon waves may be of great value in for example, the differential diagnosis of ventricular tachycardia and atrial or nodal tachycardia with associated intraventricular conduction defect, since there should be either regular cannon waves or none at all in the supraventricular tachycardias, whereas the A-V dissociation of ventricular tachycardia may give rise to sporadic cannon waves.

The worth of the jugular pulse in the diagnosis of tricuspid stenosis and insufficiency constrictive pericarditis or endocarditis pulmonary stenosis, pulmonary hypertension and right heart failure is well founded and need not be stressed here.

It is not claimed that routine recording of the jugular pulse will be of great prag



Fig. 1 Cardboard indicator taped to the neck to amplify the venous pulse.



Fig 2 Selenium photocell.

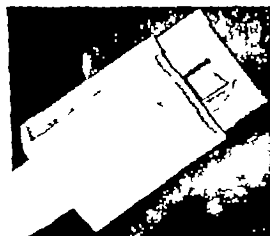


Fig 3 Photocell mounted in match box. The sliding cover varies the area of exposure.

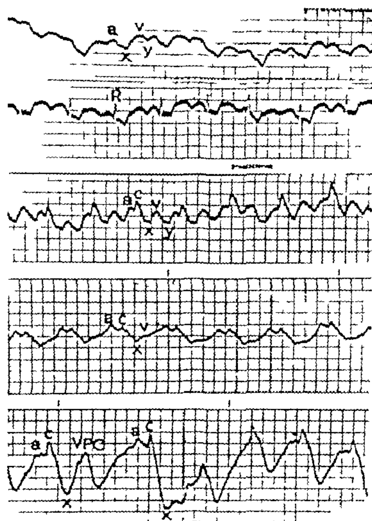


Fig. 4. Representative jugular pulse tracings obtained by the photoelectric technique described in the text (paper speed 25 mm. per second). The upper two tracings are from the same subject before and after addition of the electrocardiogram to the record for timing.

matic value in office practice. However, for those interested in perfecting their powers of physical diagnosis, a simple and readily available means of graphically recording what is seen in the neck should provide the same impetus to learning as phonocardiography has done in auscultation of the heart.

Summary

A simple and inexpensive method of tracing the jugular venous pulse using a standard electrocardiograph is described. Several examples of tracings recorded by this method are presented, and the value of the tracing as a guide in improving one's ability to analyze the pulse waves by inspection is discussed.

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The relationship of pulse pressure and diastolic pressure to systolic pressure in healthy subjects, 20-94 years of age

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The magnitude of the pulse pressure constitutes one of the basic clinical determinations for evaluation of myocardial function, disease of the heart valves, and other hemodynamic derangements. The purpose of the current study was to develop quantitative criteria for pulse pressure throughout the normal range of blood pressure by a detailed study of the systolic-diastolic pressure relationship. The statistical data have been gathered from a very large number of apparently healthy people from 20 to 94 years of age.

In the literature, the customary statements concerning pulse pressure are that "normal" values in the adult may range from 20 to 60 mm. Hg[1] or 40 to 70 mm. Hg[2] or 30 to 50 mm. Hg[3] However, a single range of values stated in this fashion is not useful in clinical medicine because, for example, a pulse pressure of 20 or 30 mm. Hg would be highly abnormal if the systolic pressure were 150 mm. Hg, since the diastolic pressure would be 120 or 130 mm. Hg, and similarly, a pulse pressure of 50 or 60 or 70 mm. Hg could not be considered to be normal if the systolic pressure were only 110 mm. Hg. Therefore, the necessity for setting standards for pulse pressure and diastolic pressure at each level of systolic pressure is apparent. The few studies[4-7] which have reported on the relationship of diastolic to systolic pressure have not received wide application.

This communication forms one facet of a larger study of blood pressure in the United States. Previous papers have dealt with the range of normal systolic and diastolic pressures separately,[8-11] the limits for hypertension,[12,13] and the relationship of systolic and diastolic pressure (separately) to age, sex, weight, height, and body build[14-16] in the same sample population used for this current analysis.

Material and methods

Data for subjects 20 to 64 years of age were derived from 74,000 unselected records of persons throughout the United States examined during World War II through industrial medical services. The other sample population, namely, persons 65 to 94 years of age, consisted of 2,298 women and 2,468 men selected from a total of 15,000 records gathered by questionnaire from physicians throughout the country. The aged patients who were chosen for analysis were "apparently healthy," viz., ambulatory, living in the community, and free of clinical evidence of cardiovascular disease or of other chronic diseases

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The arrangement of data for determination of systolic-diastolic pressure relationship was performed by use of punch cards and machine tabulation. Systolic pressures were grouped into class intervals of 10 mm. Hg as follows: 85 to 94 mm. Hg, 95 to 104 mm. Hg, etc. A tabulation was then made of the frequency with which diastolic pressures fell within each class interval of systolic pressure. In order to test the relationship between the diastolic and the systolic pressure, correlation coefficients were determined, an analysis of variance was performed, and logarithmic plots of the data were made. These procedures demonstrated that the diastolic pressure varied in an essentially linear fashion with the systolic pressure. Correlation coefficients averaged .626 for men and .621 for women for the entire population studied (range of .423 to .722). Since the coefficient of correlation is used to test the closeness of relationship between the diastolic and the systolic pressures, values such as these, although by no means indicating perfect relationship, are reasonably high for such biologic data. Regression equations which enabled the determination of the average diastolic pressure at each level of systolic pressure were then calculated for the expression of this linear relationship separately for each sex and in 10-year age groups. In order to express variability of the diastolic pressure at each level of systolic pressure, the standard error (S.E.) of the regression equation was determined. This calculation of variability was then checked against the individual mean and standard deviations of the frequency distributions of diastolic pressure at each level of systolic pressure (marginal distributions). The use of the standard error, i.e., a single value for the entire range of systolic pressure, was found to closely approximate that which would have been obtained if the second and more detailed calculation had been performed, i.e., marginal distribution, although the former did result in a somewhat wider range when systolic pressure was low and in a narrower range at high levels of systolic pressure. These two methods, standard error and marginal distribution, however, did not differ by more than 5 mm. Hg at the extremes. Two ranges of variation were then calculated from the standard error: a middle 80 per cent range (± 1.28 S.E.) and a middle 95 per cent range (± 2 S.E.).

Pulse pressures were calculated from the above-mentioned data (systolic minus diastolic pressure) at each level of systolic pressure and for each sex and in 10-year age groups.

Results

Fig. 1 shows the distribution curves of diastolic pressure (abscissa) at successive 20-mm. Hg intervals of systolic pressure. These are the "marginal distributions" which have been plotted for each 10-year age group and separately for each sex. Note that in both sexes and at all ages, as the systolic pressure increases, the modal (peak) diastolic pressure rises. The frequency distribution curves of diastolic pressure are essentially bell shaped throughout the range of systolic pressure, although a somewhat bimodal configuration (i.e., two peaks) appears in some age groups at or above a systolic pressure of 160 mm. Hg. The bimodal (double-peaked) curves occur only at hypertensive levels of systolic pressure. One peak appears at a diastolic pressure of 90 mm. Hg, whereas the second peak occurs at 110 to 120 mm. Hg. The appearance of two distinct peaks in a frequency distribution curve is generally interpreted as indicating the presence of two different groups within the population. One group (first peak) seems to display systolic hypertension alone with relatively normal diastolic pressure, whereas the population comprising the second peak shows both systolic and diastolic hypertension.

A comparison of the males and females at all ages shows no consistent difference, indicating that the relationship of systolic to diastolic pressure is the same in the two sexes.

Regression equations of diastolic pressure against systolic pressure are shown in Table I for each sex separately and by 10-year age groups. These equations express the relationship of the diastolic to the systolic pressure throughout the observed range of systolic pressures encountered. Fig. 2 shows a graphic presentation by 10-year age groups, of the regression

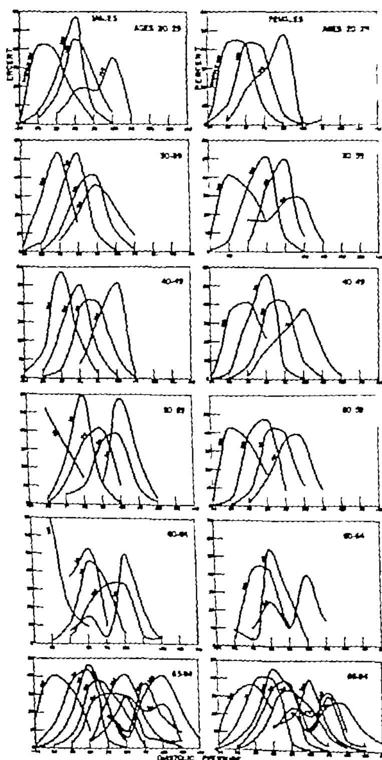


Fig. 1. These curves, which represent the percentage distribution of diastolic pressure at 20-mm.Hg intervals of systolic pressure (marginal distributions) in males and females in 10-year age groups, are in the majority essentially bell shaped in configuration. Note the regular progression toward the right increasing with levels of advancing systolic pressure. Note also the essential similarity between the sexes.

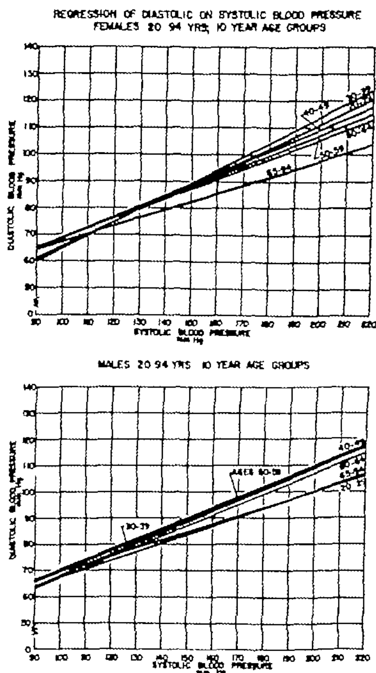


Fig. 2. Regression lines of diastolic on systolic pressure for males and for females from ages 20-94 years, showing the average diastolic pressure at each level of systolic pressure. The relationship between the systolic and diastolic pressure changes very little with age except for the age group 65-94 years, in which the diastolic pressure is lower at all levels of systolic pressure than at younger ages.

equations enabling one to calculate the mean diastolic pressure at each level of systolic pressure. The first term of the regression equation (Table I) determines the slope or rate of rise of the regression line. This indicates that in males the diastolic pressure rises about 4 mm Hg for each 10-mm Hg increment in systolic pressure. The value is somewhat lower in the 20-29-year age group and also in the oldest group 65-94 years. In females there is a similar only slight change with age since the rate of rise in diastolic pressure is about 4.5 mm Hg for each 10 mm Hg of systolic pressure in the younger age groups, whereas in the 65-94-year age group the

Table I Regression equations for the determination of average diastolic blood pressure for any known systolic pressure

Age (yr)	Male	S.E.	Female	S.E.
20–29	D* = 304 S† + 39 1	± 8 6	D = 468 S + 18 7	± 7 6
30–39	D = 411 S + 27 0	± 8 3	D = 494 S + 15 7	± 7 9
40–49	D = 401 S + 30 3	± 7 9	D = 438 S + 23 5	± 7 7
50–59	D = 404 S + 29 1	± 8 3	D = 403 S + 28 4	± 8 4
60–64	D = 399 S + 27 3	± 9 1	D = 375 S + 31 1	± 9 9
65–94	D = 340 S + 32 4	± 9 9	D = 292 S + 38 9	± 10 5

S.E. Standard error.
*Diastolic blood pressure
†Systolic blood pressure.

Table II Average diastolic and pulse pressure for each level of systolic pressure for both sexes

Systolic pressure (mm Hg)	Age 20-64 yr		Age 65 94 yr	
	Diastolic pressure (mm Hg)	Pulse pressure (mm. Hg)	Diastolic pressure (mm Hg)	Pulse pressure (mm Hg)
90	64	26	62	28
100	68	32	65	35
110	72	38	68	42
120	76	44	72	48
130	80	50	75	55
140	84	56	79	61
150	88	62	82	68
160	92	68	85	75
170	96	74	89	81
180	100	80	92	88
190	104	86	95	95
200	108	92	99	101
210	112	98	102	108
220	116	104	106	114

rate of rise in diastolic pressure is only 3 mm.Hg for each 10 mm Hg of systolic pressure

Table II shows the actual values for "normal" diastolic pressure and pulse pressure at each level of systolic pressure, for both sexes divided into two basic age groups, 20-64 years and 65-94 years. The sexes are combined in this table because we found no essential sex difference. These values have been rounded off to the nearest millimeter of mercury and differences among age groups have been eliminated where they proved to be too small to be of practical significance. Hence there is one set of values for both sexes in the age group 20-64 years and another for the age group 65-94 years. Standard error of the regression equation is 8 mm Hg for the 20-64-year age group and 10 mm Hg for the older age group From these data, two ranges of variation have been calculated a middle 80 per cent range (±1 28 S E.) and a middle 95 per cent range (±2 S E.) as shown in Tables III and IV The limits of the middle 80 per cent (±1.28

Table III. Middle 80 per cent range ("normal" range) of diastolic pressure for each level of systolic pressure for both sexes

Systolic pressure (mm. Hg)	Age 20-64 yr — Diastolic pressure (mm. Hg)		Age 65-94 yr — Diastolic pressure (mm. Hg)	
	Lower limit	*Upper limit*	*Lower limit*	*Upper limit*
90	54	74	49	73
100	58	78	52	78
110	62	82	55	81
120	66	86	59	85
130	70	90	62	88
140	74	94	66	92
150	78	98	69	95
160	82	102	72	98
170	86	106	76	102
180	90	110	79	105
190	94	114	82	108
200	98	118	86	112
210	102	122	89	115
220	106	126	93	119

Table IV. Middle 95 per cent range ("abnormal" range) of diastolic pressure for each level of systolic pressure for both sexes

Systolic pressure (mm. Hg)	Age 20-64 yr — Diastolic pressure (mm. Hg)		Age 65-94 yr — Diastolic pressure (mm. Hg)	
	Lower limit	*Upper limit*	*Lower limit*	*Upper limit*
90	48	80	42	82
100	52	84	45	85
110	56	88	48	88
120	60	92	52	92
130	64	96	55	95
140	68	100	59	99
150	72	104	62	92
160	76	108	65	95
170	80	112	69	109
180	84	116	72	112
190	88	120	75	115
200	92	124	79	119
210	96	128	82	122
220	100	132	86	126

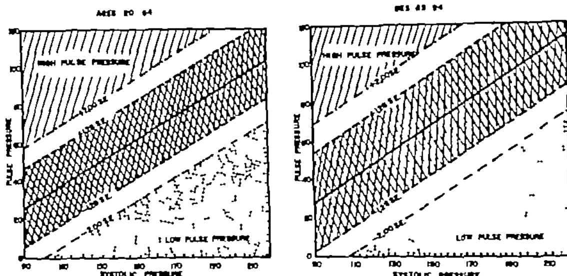


Fig. 3. In this figure, the average and proposed limits of variation of pulse pressure at all levels of systolic pressure for males and females are illustrated separately for age groups 20-64 years and 65-94 years. The central heavy line represents the average pulse pressure whereas the cross-hatched area encloses the range of "normal" variation (central 80 per cent or ± 1.28 S.E.). Zones of abnormally high and low pulse pressure (beyond the central 95 per cent limits ± 2 S.E., are labeled. Note that in the older age group, the average pulse is higher and the range of "normal" variation wider than in the younger ages.

S.E.) range may be taken as enclosing the "normal" range of variation. Values greater or lower than the limits of the middle 95 per cent (±2 S.E.) range are almost certainly abnormal, whereas those falling between the middle 80 per cent range and middle 95 per cent range may be abnormal. For the 20-64-year age group the middle 80 per cent range of diastolic or pulse pressure for each level of systolic pressure can be determined by adding to or subtracting from the average values shown in Table II 10 mm.Hg (±1.28 S.E.) and 16 mm Hg for the middle 95 per cent range (±2 S.E.). For the 65-94-year age group, 13 mm.Hg on either side of the average will define the limits of the middle 80 per cent range (±1.28 S.E.) and ±20 mm Hg the middle 95 per cent range (±2 S.E.). The average values for middle 80 per cent range and 95 per cent range for pulse pressure are shown in Fig. 3. Note that in the younger age group the average pulse pressure (heavy continuous line, Fig. 3) increases threefold in magnitude when the systolic pressure increases from 90 to 220 mm. Hg and more than fourfold in the older age group. In the age group 20-64 years, subjects with a systolic pressure of 90 mm. Hg have on the average a diastolic pressure of 64 mm.Hg and pulse pressure of 26 mm Hg. Those with a systolic pressure of 140 mm Hg have an average diastolic pressure of 84 mm.Hg and pulse pressure of 56 mm.Hg. At a systolic pressure of 160 mm Hg the average diastolic pressure is 92 mm.Hg and the average pulse pressure is 68 mm Hg, whereas with a systolic pressure of 200 mm.Hg the average diastolic pressure is 108 mm.Hg and the average pulse pressure is 92 mm Hg. For the age group 65-94 years the average diastolic pressure at each level is a little lower, the pulse pressure is greater, and the range of variation is wider. Thus, with a systolic pressure of 140 mm Hg the average diastolic pressure is 79 mm.Hg and the average pulse pressure is 61 mm.Hg and at a systolic pressure of 200 mm Hg the average diastolic pressure is 99 mm Hg and the average pulse pressure is 101 mm.Hg.

Discussion

This study has defined the relationship of systolic pressure to diastolic pressure and pulse pressure throughout the range of pressures which are encountered in an

essentially random ambulatory population from which individuals with clinically apparent heart disease have been excluded. Confirming the observations of others,[4,5] we found that systolic and diastolic pressures varied in an essentially linear fashion. This relationship was expressed in terms of a regression equation. In both sexes for age group 20-64 years (Table II) diastolic pressure was found to increase by about 4 mm Hg for each 10-mm Hg increase in systolic pressure, whereas in the older age group of 65-94 years the diastolic pressure increased 3 mm Hg for each 10-mm Hg increment in systolic pressure. Pulse pressures thus progressively widened as the level of systolic pressure increased, quadrupling in magnitude between the extremes of the systolic pressure range (90 to 220 mm Hg). Thus there is no single value possible for "normal" pulse pressure which can cover the entire range of pressures observed. For example, a pulse pressure of 30 mm Hg which would be "normal" if the subject's systolic pressure were 100 mm Hg would be highly abnormal if the subject's systolic pressure were 150 mm Hg. Similarly, a pulse pressure of 60 mm Hg would be "normal" at a systolic pressure of 150 mm Hg, but too low with a systolic pressure of 220 mm Hg.

The usual physiologic explanation presented for the fact that a single level of pulse pressure is not maintained throughout the range of blood pressure but does progressively increase as systolic pressure increases can be found in the elasticity characteristics (compliance) of the wall of the aorta and central arteries. Compliance of the aortic wall is known to decrease progressively as the internal distending pressure increases,[16,17] causing widening of the pulse pressure. Furthermore, aortic compliance at older ages is less at each level of systolic pressure than at younger ages,[17] thus accounting for the widened pulse pressure at all levels of systolic pressure in apparently healthy subjects of older age. Other factors which influence pulse pressure, such as stroke volume, heart rate, and peripheral vascular resistance, are not believed to be responsible for widening of the pulse pressure with *advancing age* or with elevation of systolic pressure.

The utility of the standards of pulse pressure described herein lies, of course, in the evaluation of cardiovascular lesions which cause widening or diminution of the pulse pressure.

Clinically, pulse pressure is widened in the following circumstances: (1) *abnormally large runoff of blood during diastole*, usually combined with large stroke volume, such as in aortic insufficiency, patent ductus arteriosus, arteriovenous fistulae; (2) *decreased elasticity* (compliance) of the aorta and major arterial branches due to aging or to premature atherosclerosis; (3) *large stroke volume*, as in bradycardia or heart block; (4) *decreased peripheral vascular resistance* and *increased stroke volume*, as in fever, thyrotoxicosis, and hyperkinetic states and beriberi.

Pulse pressure is narrowed in the following circumstances: (1) *reduced stroke volume*, as in tachycardia, myxedema, poor myocardial function (myocarditis, advanced atherosclerosis), shock, pulmonary stenosis, aortic stenosis, or mitral stenosis; (2) *obstruction to left ventricular or aortic outflow* due to aortic stenosis or to coarctation of the aorta.

Summary

The relationship of systolic pressure to diastolic pressure and pulse pressure has been studied in more than 20,000 apparently healthy subjects ranging in age from 20 to 94 years, for the purpose of developing quantitative standards of normal pulse pressure throughout the range of blood pressure.

Diastolic pressure and pulse pressure were found to vary linearly with the systolic pressure, and regression equations expressing this relationship have been presented. No significant sex difference was found. However, in both sexes, advancing age resulted in a widening of the pulse pressure and related lowering of the diastolic pressure at all levels of systolic pressure. Thus at ages 20-64 years, diastolic pressure increases about 4 mm Hg and pulse pressure widens by 6 mm Hg for each 10-mm Hg rise in systolic pressure, whereas at ages 65-94 years, diastolic pressure increases 3 mm Hg and pulse pressure widens by 7 mm Hg for a comparable change in systolic pressure. Hence

the pulse pressure virtually quadruples when systolic pressure increases from 90 to 220 mm Hg. Limits of normal variation have been presented. These quantitative standards should prove to be useful in the evaluation of cardiovascular diseases or hemodynamic abnormalities which affect the pulse pressure.

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Mode of onset of atrial fibrillation in man

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The mechanisms responsible for the initiation and maintenance of atrial fibrillation (AF) have been matters of continuing controversy and investigation. In the experimental animal AF may be induced by the application of drugs or chemicals to the atrial wall,[1,2] by direct electrical stimulation at a rapid rate,[3] or by a single electric shock properly timed during the relative refractory phase.[4-7] These techniques have yielded much important information concerning the electrophysiologic characteristics of fibrillation. Their application to an understanding of the mode of onset of spontaneous AF in man, however, remains moot.

Since the first electrocardiogram showing the onset of AF was illustrated in 1918,[8] a number of tracings have been published which suggest that an atrial premature contraction (APC) may immediately precede the onset of AF.[9-12] Clinically, it is recognized that frequent APCs may signal impending AF. Although this association is frequently alluded to,[13,14] no clinical quantitative data have been brought together to further characterize the development of AF in man.

Recently, we have had the opportunity to observe 14 instances of spontaneous reversion from sinus rhythm to AF and 4 examples of atrial flutter changing to AF in patients with heart disease during continuous electrocardiographic monitoring. This communication will describe the electrocardiographic findings during the onset of AF in these patients. The electrocardiograms from the group who developed AF were compared to tracings from similar patients who had multiple APCs but did not develop AF. The significance of the APCs and the importance of the degree of prematurity of an APC to the subsequent initiation of AF will be discussed.

Methods and materials

Eighteen episodes of relapse from sinus rhythm to AF were observed in 14 patients. In 15 instances in 11 patients the relapse occurred within minutes after successful D.C. precordial shock for reversion to sinus rhythm from AF. Two episodes of onset of AF were recorded during a routine electrocardiogram. One occurred during carotid sinus massage.

The patients ranged in age from 33 to 70 years. Seven had rheumatic heart disease, 1 had idiopathic myocardial hypertrophy, 3 had arteriosclerotic heart disease. In 3, no evidence of heart disease was found except for AF. In the patients undergoing electrical reversion, AF had

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been present from 3 weeks to 15 years. All had taken digitalis on a long term basis either for control of ventricular rate or for symptoms of congestive heart failure.

The electrical reversion was conducted according to a protocol described elsewhere.[8] Intravenous thiopental sodium anesthesia, in doses of 200 to 450 mg., was administered prior to synchronized D.C. shock. Six patients had received 0.4 to 1.2 Gm. of quinidine in the 12-hour period prior to conversion. One patient received 0.8 mg. of atropine 1 hour prior to reversion. After D.C. shock, electrocardiograms were monitored for at least 10 minutes, and in some patients for 30 minutes or more. In several patients an endocardial atriogram was obtained.[16]

For purposes of comparison electrocardiograms recorded under similar circumstances, after reversion from AF to sinus rhythm by D.C. shock, were reviewed from another group of 20 patients in whom frequent APCs (14 patients) or transient atrial tachycardia (6 patients) occurred. These patients were clinically similar to those in whom sinus rhythm reverted to AF except that sinus rhythm was maintained despite the ectopic beats.

To determine the relative prematurity of ectopic beats, P waves were identified and P-P intervals measured. The prematurity of an individual APC is expressed as the ratio of the coupling interval to the preceding cycle length or

$$\text{Coupling index} = \frac{\text{coupling interval}}{\text{preceding cycle length}} = \frac{P - P'}{P_1 - P_2}$$

where P′ represents the APC, P_2 the immediately preceding atrial discharge, and P_1 the atrial discharge immediately preceding P_2. Since significant depression of the sinus pacemaker was noted to follow APCs in some patients, the true preceding atrial cycle length and therefore the relative prematurity of the APC was not considered to be accurately gauged by this method in the presence of atrial bigeminy.

Results

Analysis of electrocardiograms recorded during the onset of AF revealed unequivocally that a premature atrial discharge preceded electrocardiographic base-line changes interpreted as AF in all 14 observations of relapse from sinus rhythm. In 4 patients the APC which initiated AF was the only one observed. In the other patients single or multiple APCs occurred prior to the APC which initiated AF.

An APC appeared to initiate AF by two different atrial responses. In 10 episodes of relapse, AF immediately developed after a readily identifiable APC (Figs. 1-4). That an APC may initiate AF is shown most clearly in Fig. 4, which depicts the onset of AF as recorded with a right atrial endocardial lead. The last P wave in the tracing is premature and is followed immediately by the rapid, disorganized atrial discharge of AF.

A second type of atrial response to an APC, the initiation of an atrial tachycardia followed by AF, was also observed. In 4 instances an APC was followed by a succession of from 2 to 5 atrial complexes at an accelerating rate culminating in AF (Figs. 3 and 5). One patient developed AF on two different occasions, once by each type of atrial response. The first time, AF appeared immediately after an APC. The second bout of AF was preceded by an atrial tachycardia initiated by an APC (Fig. 5).

The mean coupling index for the 14 APCs which appeared to initiate AF was .48. Nine had a coupling index of less than .50 and in only 1 was it greater than .60 (Fig. 5). The ranges of the coupling indices for those APCs immediately preceding AF and those initiating a short burst of atrial tachycardia followed by AF were similar (Figs. 5 and 6).

To evaluate the significance of the degree of prematurity of an APC to the subsequent onset of AF, the coupling indices of three groups of APCs were compared: *Group 1*, APCs followed by AF; *Group 2*, APCs not followed by AF in the patients who subsequently developed AF; and *Group 3*, APCs in a group of 20 patients who did not develop AF and who were studied under conditions entirely similar to those for the patients with AF.

The results are depicted in Fig. 6. In Group 1, the mean coupling index was .48 ± .03 (S.E.M.). In Group 2, the mean coupling index was .65 ± .02. In

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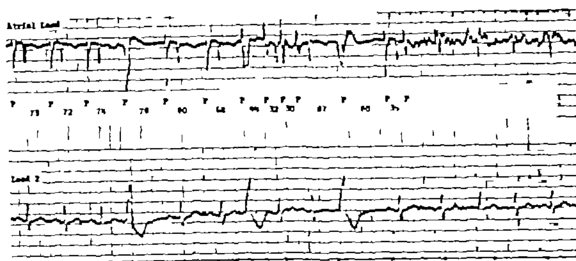


Fig. 4 Simultaneous right endocardial atriogram and Lead II from 53-year-old man, D F with mitral regurgitation after D C precordial shock for long-standing atrial fibrillation. The fourth, seventh, and tenth QRS complexes are ventricular premature complexes. P-P intervals are recorded between the upper and lower strips (decimal omitted). The eighth P wave is premature, coupling index 65 and is followed by 2 more premature P waves at an accelerating rate. The next 2 P waves are apparently sinus The last P wave is premature coupling index 45 is not conducted to ventricles, but initiates rapid disorganized atrial activity characteristic of atrial fibrillation.

Group 3 the mean coupling index was 68 ± 01 The difference between the means of Group 1 and those of both Groups 2 and 3 is highly significant ($p < 001$) The mean coupling indices for Groups 2 and 3 are virtually identical.

These data are interpreted as indicating that the capacity of an APC to initiate AF is directly related to the degree of prematurity as expressed by the coupling index. When an APC has a coupling index of less than .50 there is a high degree of probability that it will be followed by AF When the coupling index is between .50 and 60 AF may occur but is less likely than maintenance of sinus rhythm. AF is unlikely when the coupling index is greater than 60

In 4 episodes of AF in 3 patients the onset of the arrhythmia appeared to have a different mechanism In these patients AF developed in the presence of atrial flutter when the atrial rate of 300 gradually increased and totally irregular more rapid atrial responses interpreted as fibrillation developed In 1 patient, atrial flutter was initiated twice after attempted D C reversion of AF In both instances the flutter became AF as the atrial rate increased In the other 2 patients the flutter was spontaneous. AF developed in response to carotid sinus massage in 1 and appeared spontaneously during the recording of a cardiogram in another

Discussion

The present study has shown that AF may develop spontaneously in man by two different mechanisms by an increase in the atrial rate in flutter and after an appropriately timed APC The significance of the timing of an APC to the subsequent initiation of AF has been revealed by comparing the coupling indices of the pre-AF APCs and the non AF APCs In the patients who developed AF the more premature APCs usually were followed by AF The importance of the degree of prematurity is shown by the fact that the mean coupling index of the APCs followed by AF was significantly less than that of the APCs not followed by AF Furthermore the mean coupling indices of the non-AF APCs in both the patients who did and those who did not subsequently develop AF were practically identical

The observation that fibrillation of the atrium may follow a properly timed APC is in harmony with recent clinical reports that ventricular premature contractions

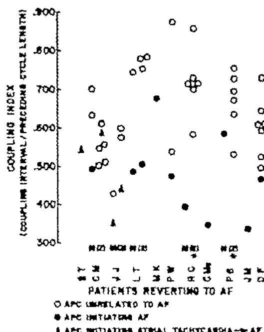


Fig 5 Coupling indices of atrial premature contractions (APC) preceding 14 episodes of spontaneous atrial fibrillation (AF) in 11 patients. Data obtained from continuous electrocardiograms recorded prior to onset of atrial fibrillation. In 3 patients, onset of AF was observed twice. In 2 patients, second set of observations ( ) followed restoration and maintenance of sinus rhythm despite multiple APCs. Note that APCs initiating AF, solid circles and triangles, have shorter coupling indices than APCs unrelated to AF.

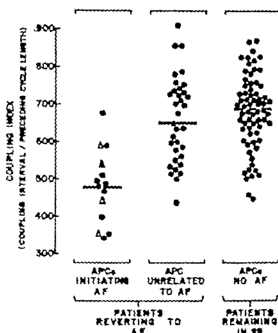


Fig 6 Coupling indices of APCs and onset of AF. In *left-hand column* are APCs initiating 14 episodes of AF in 11 patients. Open triangles represent APCs followed by atrial tachycardia accelerating to AF. *Middle column* depicts APCs unrelated to AF in same patients. *Right hand column* shows APCs from 20 patients who did not develop AF (*See text for details.*) Horizontal bars mark mean for each group. The mean coupling index of APCs initiating AF is significantly smaller ($p < .001$) than the mean for the two groups of APCs not related to AF. The mean coupling index for the two groups of APCs not related to AF are not significantly different.

occurring during the T wave or relative refractory period of the previous ventricular beat are associated with the development of ventricular fibrillation.[11-14] The demonstration for both atrium and ventricle that a spontaneous ectopic discharge has the capacity to initiate fibrillation if appropriately timed relative to the preceding cycle is consistent with the experimental delineation of atrial and ventricular vulnerability.[7,19]

It has been demonstrated in many laboratories that a single pulsed discharge of appropriate duration and amplitude will precipitate fibrillation if administered during the relative refractory period of the atrium or ventricle.[4,7,19-22] Stimulation of the atrium during other portions of the cardiac cycle does not result in AF. That portion of the relative refractory period during which susceptibility to fibrillation is high has been termed the vulnerable period.

Vulnerability has been considered to be an intrinsic property of normal ventricular myocardium.[22] Maintenance of persistent fibrillation in the atrium is more difficult experimentally than in the ventricle. This may be related in part to the different hemodynamic consequences of fibrillation in the pump as compared to the pump primer. The importance of sufficient myocardial mass, the mean duration of the refractory period and the mean conduction velocity to sustain fibrillation has been emphasized.[23,24]

The onset and maintenance of atrial

fibrillation is enhanced by vagal stimulation or the administration of cholinergic drugs.[7] Vagal effects have been shown to be nonuniformly dispersed in the atrium[18] and nonuniform distribution of recovery and excitation is considered to be one of the prime requisites for the development of fibrillation.[14] Varying degrees of sympathetic and parasympathetic activity may well have occurred in the patients in this study who developed APCs after barbiturate anesthesia and precordial D.C. shock. No differences in the characteristics of the three groups of patients whose electrocardiograms were analyzed were apparent, however, save for the fact that those who developed AF had the more premature APCs.

Those mechanisms which precipitate AF are not necessarily the same as those which maintain it. It has been postulated that AF is a self-sustaining arrhythmia. In a mathematical model it has been shown that a single properly timed premature stimulus could in the presence of adequate dispersion of recovery times lead to total disruption of the depolarizing wave front and self-perpetuating atrial fibrillation.[14]

Others have suggested that fibrillation is maintained by a rapidly firing ectopic center.[1-24] A repetitive electrical stimulus may drive the atrium so rapidly that failure of coordinated response and atrial fibrillation ensue.[5] Evidence has been reported that acute AF initiated by a single electrical stimulation is sustained by rapid *focal discharges*.[17] Ventricular fibrillation induced by a single shock in the vulnerable *period appears to be triggered by a series* of accelerating discharges from the stimulus focus.[13] Since single-shock electrical stimuli which are followed by AF must exceed the threshold which would produce only an APC, persistence of an ectopic focus at a rapid rate during the subsequent AF may be related to local injury.

The techniques utilized in the present study were not adequate to evaluate the possibility that the AF which developed in our patients was associated with a persistent rapid focal discharge. Analysis of a scalar electrocardiogram recorded at slow speed with a machine of low-frequency response provides only relatively crude information about atrial events. Acceleration of atrial flutter or atrial tachycardia is consistent with, but does not prove the theory of focal discharge.

After a properly timed APC an accelerating atrial discharge for a few beats (less than 6) culminating in AF was noted four times in 3 patients. Characteristic electrocardiographic flutter was not observed to follow an APC. The development of AF may follow stretching of the atrium in experimental flutter or carotid sinus (vagal) stimulation in naturally occurring flutter as observed in 1 patient and reported by others.[21,31] Vagal stimulation is known to shorten the atrial refractory period.[18] In both circumstances, alteration of electrophysiologic properties of the atrium in the presence of a rapid ectopic focus results in loss of coordinated atrial depolarization and AF.

Thus, both experimental data and the observations reported herein suggest that AF may follow a properly timed premature contraction or an accelerating tachycardia. It seems reasonable to assume that the onset of AF has the same mechanism in both instances. Evidence in favor of the thesis of fractionation of the depolarization front due to nonhomogeneous distribution of recovery and conductivity and multiple wavelet formation has been cited. The possibility of circus movement or a persistent and very rapid ectopic focus cannot be evaluated, however, from our data.

There have been many attempts to promulgate a unified theory of atrial arrhythmias by relating the tachycardias to discharge of a single focus at different rates depending on the rhythm.[19] APCs, ectopic atrial tachycardias, and atrial flutter are considered to differ only by the rate of ectopic discharge. *Recent* reports suggest that atrial flutter in man may have two mechanisms: a single ectopic focus and a circus movement.[31,32] It has hitherto been difficult to fit AF into a unified theory of arrhythmias since it seems to be unlikely that a single ectopic focus could remain active at a rapid rate for many years and perpetuate AF.

Our observations linking the onset of spontaneous AF in man to focal ectopic activity are compatible with a unified

theory of atrial arrhythmia. Thus, atrial tachycardias represent continuous discharge of single foci which discretely have the capacity to produce APCs. Atrial flutter is probably unifocal in origin in some instances. Acceleration of the rate of discharge may, under certain anatomic and physiologic conditions, be followed by AF. More commonly, a single APC, properly premature, initiates AF in the diseased heart as a consequence of intrinsic electrophysiologic properties described as "vulnerability." Thus it is possible to link the genesis of the atrial arrhythmia to ectopic focal discharge. The mechanism of initiation in the case of AF and possibly flutter is unrelated to maintenance. Maintenance of AF will depend on interrelationships between atrial size, conduction, and recovery, but is not dependent on the initial trigger.

Summary

The mode of onset of atrial fibrillation has been recorded 18 times in 14 patients during continuous monitoring of an electrocardiogram. An atrial premature discharge preceded the onset of atrial fibrillation in all 14 episodes of relapse from sinus rhythm. In 10 of these the premature P wave was followed immediately by atrial fibrillation. In 4 the premature P wave appeared to initiate a brief run of atrial tachycardia (less than 6 beats) which accelerated to atrial fibrillation.

In 4 observations atrial fibrillation developed from established atrial flutter. The atrial rate gradually accelerated from approximately 300 per minute, and irregular, rapid atrial response characteristic of atrial fibrillation appeared. In 1 patient this event occurred during carotid sinus massage.

The relative prematurity of ectopic atrial beats was evaluated by calculating the coupling index, defined as the ratio of the coupling interval (P-P) to the preceding cycle length. The mean coupling index of the 14 atrial premature contractions which initiated atrial fibrillation was .48 ± .03 (S.E.M.). The mean coupling index for atrial premature contractions which were not followed by atrial fibrillation was .65 ± .02 in the patients who subsequently developed atrial fibrillation and .68 ± .01 in a similar group of patients with ectopic atrial activity who did not develop fibrillation. The difference between the mean coupling indices of those P waves which initiated atrial fibrillation and those which did not is highly significant ($p < .001$).

It is concluded that a spontaneously occurring atrial premature impulse may initiate atrial fibrillation. In some instances the fibrillation is preceded by an accelerating atrial tachycardia. The propensity of a premature impulse to initiate fibrillation is related to its relative prematurity, expressed as the coupling index. When the coupling index is less than .50 the chance of atrial fibrillation is high; when it is greater than .60 the chance of atrial fibrillation following that particular premature P wave is small.

The observation that atrial fibrillation may follow a properly timed ectopic discharge is consistent with the experimental delineation of an atrial vulnerable period. Possible relationships between focal ectopic activity, atrial tachycardias, and atrial fibrillation are discussed.

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Exercise performance and stroke volume changes in two patients with constrictive pericarditis

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Constrictive pericarditis is a disease in which the cardiac chambers and great vessels are encased in a rigid fibrous sheath. As a result, the diastolic inflow of blood is impaired. Ventricular pressure-volume relationships are altered significantly.[1] At rest, intracardiac pressures are elevated. Cardiac output may be slightly reduced or normal but usually rises only by means of an increase in the heart rate.[2] During exercise, the increase in output is restricted and augmentation of stroke volume is *seldom found*.[3]

During the past year, 2 patients with constrictive pericarditis were studied at Wilford Hall USAF Hospital. Prior to operation, exercise produced surprising *increases* in cardiac output and stroke volume. This report will attempt to explain how such hemodynamic changes can occur in a disease characterized by limited diastolic filling.

Methods

Right heart catheterization was performed in the usual manner. Arterial blood was sampled from an indwelling Cournand needle in one procedure. In the others, retrograde catheterization of the left ventricle was performed percutaneously from the left femoral artery, using a modified Seldinger technique.[4] Cardiac output was determined by the Fick method. Patients were exercised in the supine position with their feet attached to the pedals of a bicycle ergometer. Exercise cardiac output was obtained between minutes 3½ and 4½, at which time a steady-state measurement was assumed. Pressures were measured with Statham transducers and transcribed on an Electronics for Medicine recorder.

Clinical summaries

Case 1. A 44-year-old lieutenant colonel was admitted to Wilford Hall USAF Hospital in October 1963. Three years previously, he had developed the abrupt onset of severe anterior chest pain aggravated by breathing. In June 1961, chest pain, dyspnea, hepatomegaly, and ankle edema had developed. At that time, cardiac enlargement was found on the x-ray film and there were nonspecific S-T and T-wave changes on the electrocardiogram. After the administration of digitalis and chlorothi-

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aside, the symptoms abated, and he remained asymptomatic for the next 2 years.

Physical examination in October 1963 revealed only a slight increase in jugular venous pressure hepatomegaly and minimal cardiac enlargement. Sinus rhythm was present. There were no murmurs or extra sounds, splenomegaly or peripheral edema. There was no paradoxical pulse

The electrocardiogram was normal. The chest x-ray film revealed minimal generalized cardiac enlargement. Calcification of the pericardium was absent. Tuberculin skin testing was nonreactive Digitalis and chlorothiazide were discontinued od cardiac catheterization was performed 10 days later Although resting intracardiac pressures were elevated and a diastolic plateau pattern was seen in both ventricular tracings, exercise cardiac output was normal (Table I) Since only a minor degree of constrictive pericarditis was suspected the patient was ad ned to return to active duty without medication.

Ten days after discharge he developed the onset of shortness of breath peripheral edema and abdominal enlargement He denied excessive physical activ ty preced ng the onset of symptoms Digitalis and chlorothiazide were einst tuted and he was eturned to Wilford Hall USAF Hospital. Physical examination and laboratory tests were unchanged from those at the time of his previous admission.

Exploratory thoracotomy was performed The pericardium was found to be extremely thick and fibrotic, but was easily removed. No tubercle bacilli were found on culture or stain of the surgical specimen. The postoperative course was uneventful *Digitalis and chlorothiazide were discontinued*

Subsequently he returned to full physical activity Cardiac catheterization was performed 3 months after operation. All pressures and outputs at rest and after exercise were normal (Table I) The diastolic plateau pattern had subsequently disappeared f om the entricular pressure tracings. The patient remains asymptomatic at present and has returned to active duty

Case 2 A 26-year-old first lieutenant was admitted to the Wilford Hall USAF Hospital in March 1963 because of progressive fatigue and dyspnea. In early 1962 he had experienced an acute febrile illness characterized by chest pain, malaise and weakness. Symmetrical T-wave inversion was noted in limb and precordial electrocardiographic leads. No pericardial friction rub was heard. In November 1962 a ventricular gallop had first been noted and in December he had been found to have hepatosplenomegaly and peripheral edema.

Physical examination in March 1963 revealed prominent distention of the neck eins The rhythm was sinus. Paradoxical pulse was not detected The lungs were clear There was no cardiac enlargement. No murmurs were heard. However a loud protodiastolic extra sound w noted t the apex. The liver was felt 7 cm. below the right costal margin

Table I Case 1 catheterization data

	Preoperative		Postoperative	
	Rest	*Exercise*	*Rest*	*Exercise*
Left ventricle (mm. Hg)	112/16	186/_2	103/6	158 12
*Pulmonary capillary (mm Hg)	$\overline{14}$	—	$\overline{6}$	—
Pulmonary artery (mm. Hg)	28/15 ($\overline{20}$)	51/28 ($\overline{40}$)	21 11 ($\overline{14}$)	37 15 ($\overline{20}$)
Right ventricle (mm. Hg)	28/12	50/14	23 6	35/7
Right atrium (mm. Hg)	$\overline{13}$	$\overline{12}$	$\overline{3}$	$\overline{4}$
Heart rate (per min.)	61	150	60	158
Ventilation (L./min.)	7 50	53 40	7 47	50 50
O consumption (/min)	242	1,682	240	1,533
Arteriovenous difference (c.c./L.)	44 5	95 2	40 4	104 7
Cardiac output (L./min.)	5 43	17 70	5 93	14 64
Stroke volume (c.)	89 3	117 2	99 0	9 7
Output rise/100 c.c. of O consumption (c. min.)		781		674

Table II Case 2 catheterization data

	Preoperative		Postoperative	
	Rest	Exercise	Rest	Exercise
Brachial artery (mm Hg)	114/76 ($\overline{93}$)	164/72 ($\overline{100}$)	—	—
Left ventricle (mm Hg)	—	—	103/8	128/10
Pulmonary artery (mm Hg)	27/17 ($\overline{21}$)	48/25 ($\overline{38}$)	23/9 ($\overline{15}$)	$\overline{20}$
Right ventricle (mm Hg)	27/18	51/23	26/7	28/8
Right atrium (mm Hg)	$\overline{17}$	$\overline{19}$	$\overline{5}$	$\overline{4}$
Heart rate (per min)	68	150	75	180
Ventilation (L./min)	8 0	69 5	8 8	77 1
O_2 consumption (c.c /min.)	236	2 120	285	1,867
Arteriovenous difference (c c./L.)	52 0	138 0	42 8	100 1
Cardiac output (L./min)	4 56	15 70	6 66	18 70
Stroke volume (c.c)	67 4	104 7	88 5	104 0
Output rise/100 c c of O_2 consumption (c c./min)		593		761

and the tip of the spleen was barely palpable. There was a trace of ankle edema.

Laboratory studies were within normal limits, with the exception of an elevated Bromsulphalein of 23 per cent and nonspecific T-wave changes on the electrocardiogram Tuberculin skin testing was nonreactive Right heart catheterization revealed considerable elevation of intracardiac pressures at rest, a diastolic plateau pattern in the right ventricle and a slight reduction in resting cardiac output (Table II) However a marked increase in output and stroke volume was noted with exercise

Thoracotomy was advised The operation revealed that thick fibrous pericardial sac completely encased the heart Cardiac pulsations were grossly diminished. However the fibrotic membrane was easily removed from the ventricles, and from caval inlets and pulmonary veins At the conclusion of the procedure the cardiac filling and pulsation seemed to be notably improved A pathologic specimen showed only dense fibrous reaction without evidence of tuberculosis. The postoperative course was uncomplicated.

The patient was readmitted in January 1964. He had returned to active duty Exercise tolerance was normal and he disclaimed symptoms. Repeat cardiac catheterization showed normal pressures and contour in the chambers on both the right and left sides at rest and with exercise. Cardiac output on exercise was comparable to that demonstrated before operation.

Discussion

Data obtained in the present study have demonstrated several important features of constrictive pericarditis (1) A normal increase in cardiac output with exercise can occur in patients with significant pericardial restriction (2) In the presence of constrictive pericarditis, stroke volume can increase significantly with exercise. (3) After operation resting stroke volume may rise but an increase with exercise may no longer occur

A number of hemodynamic changes have been demonstrated previously in constrictive pericarditis. In general the magnitude of these changes has been related to the duration of disease the severity of the restriction and the amount of associated myocardial damage

Consistent elevation of intracardiac pressures has been present and further rises in pressure have been found with exercise[5,6] A characteristic contour has invariably been seen in the ventricular pressure tracing[7] However this contour

the diastolic plateau is not specifically diagnostic because it has been found in other cardiac diseases.[3-6]

Measurements of resting output in constrictive pericarditis have been normal or low.[8-11] Preoperatively, an appropriate rise in output with exercise has been reported only occasionally,[12] and such rises were not usually accompanied by increases in stroke volume.[8] However, a number of patients studied after pericardiectomy have demonstrated a rise in stroke volume at rest,[9] and Johansson[9] has suggested that this finding may be the best evidence of a successful surgical result.

In some patients the possibility of associated myocardial failure has been suggested pathologically by the finding of fibrocalcific invasion of the myocardium at operation[13-15] and by evidence of myocardial atrophy at autopsy.[16,17] Myocardial failure has been suspected when patients with constrictive pericarditis responded favorably to digitalis therapy[18] or when low cardiac output persisted after seemingly adequate surgical procedures.[19]

The large rises in output with exercise in these patients, therefore, were unexpected. A normal response to exercise has been determined in patients without heart disease by relating the increase in oxygen consumption to the change in cardiac output. For each 100 c.c. increase in consumption a 600 to 800 c.c. increase in flow is expected.[20] Both patients, therefore, had essentially normal responses to exercise before as well as after pericardiectomy (Tables I and II).

The rise in cardiac output with exercise was accomplished primarily through an increase in stroke volume. The majority of recent studies in normal human subjects exercising while supine and in animals show no appreciable rises in stroke volume.[21-27] However, significant exceptions were found by Friedman[28] and Musshoff[29] and associates, who noted increases in stroke volume of as much as 50 to 60 per cent in patients exercising in the supine position. Experimental studies indicate that changes in stroke volume are more likely to develop in subjects exercising in the upright position,[24,25,30] and are most marked at the onset of work and at maximal exercise.[22,30] The significant increase in preoperative exercise stroke volumes observed in this study has seldom been found in patients with other forms of heart disease severe enough to necessitate cardiac surgery.[21,31,32]

The hemodynamic studies indicate that myocardial function in these patients was normal prior to operation. Their response to exercise may have been due to less significant epicardial involvement and to a lack of myocardial extension of the disease process. Such responses have been recorded infrequently in the literature. This suggests that the majority of patients with constrictive pericarditis may have more severe involvement impairing both diastolic filling and systolic contraction. The importance of these findings lies in the possibility that a similar response to exercise may differentiate constrictive pericarditis from the various forms of cardiomyopathy giving similar rises in pressure and pulse contour abnormalities.

The reason for such a rise in stroke volume in patients with significant pericardial constriction is suggested by these studies. Inasmuch as inflow is limited, the normally functioning myocardium adapts itself by a more forceful systolic effort. While increasing contractility, it decreases its end-systolic volume, and more blood per beat is ejected. Lessened residual ventricular volume should prevent an increase in filling pressure on exercise, and, in fact, during exertion only small rises in pressures were noted. When diastolic restriction was eliminated by pericardiectomy, resting stroke volume rose considerably. On exercise, no further increase was shown, presumably because the stimulus to augment stroke volume was eliminated.

Such reasoning does not explain the recurrent edema and dyspnea in Patient No. 1. It is possible that continued effort in the upright position exceeded his ability to increase cardiac output by means of rate and stroke volume, and that pulmonary and systemic congestion ensued. A further increase in intracardiac pressure may also have been necessary to maintain diastolic filling in the upright position. The role of discontinuation of digitalis and chlorothiazide is not clear, althou

a subsequent increase in blood volume after cessation of diuretics may have augmented congestive symptoms.

The precise mechanisms of the changes exhibited in contractility are not clear. Sarnoff and Mitchell[33] have shown that ventricular performance is increased significantly by catecholamines released at nerve endings by sympathetic stimulation. On the other hand, Mommaerts and Langer[34] have suggested that, although adrenergic substances undoubtedly affect contractility, an intrinsic autoregulating property of cardiac muscle may operate independently.

Interestingly, the change in myocardial performance demonstrated in these patients before operation occurred in conjunction with an increased systemic or left ventricular systolic pressure. Heart rates and stroke volumes with exercise were similar before and after pericardiectomy, although postoperative rises in systemic or left ventricular pressures were not so great. Such rises in pressure before operation suggest that a greater sympathetic response and catecholamine effect may have been present. If a parallel may be drawn between the animal experiments of Sarnoff and associates[35] and the patients in this study, a form of homeometric autoregulation of the intact heart may have occurred. In the isolated heart this property is defined as maintenance or augmentation of work during increasing cardiac rates and peripheral resistances, occurring without an increase in ventricular fiber length. From a constant myocardial fiber length imposed by pericardial restriction, an increase in cardiac catecholamine could result in greater stroke work and volume through a shift to a new and more efficient ventricular performance curve.

Regardless of the mechanisms involved, both of these patients represent a symptomatic but functionally mild form of cardiac disease in which inflow is restricted but myocardial performance under stress is adequate. Their response to exercise has indicated normal ventricular function and an excellent prognosis.

Summary and conclusion

In 2 patients studied by cardiac catheterization the diagnosis of constrictive pericarditis was confirmed. Both responded with normal increases in cardiac output during exercise. This response was unusual because significant increases in stroke volume occurred. Pericardiectomy was performed and subsequent hemodynamic studies were normal. Although postoperatively the exercise performance was again appropriate, no increase in stroke volume occurred. However, resting stroke volume did increase. The studies show that normal ventricular function can occur in constrictive pericarditis and suggest a means of cardiac compensation in this disease. It is assumed that prior to operation the heart adapted to inadequate filling by decreasing residual volume. After removal of the obstruction to inflow such adaptation was unnecessary. The prognosis in these patients seems to be excellent because the myocardium was normal and the diseased pericardium was effectively removed.

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Experimental and laboratory reports

The ultralow-frequency ballistocardiogram in atrial septal defect

A semiquantitative approach based on the analysis of the velocity curve

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Using the high frequency method of Starr Henderson[1] found abnormalities in the ballistocardiograms (BCG) of 26 of 34 patients suffering from atrial septal defect A high H peak alone was seen especially in the cases which showed no increase in pressure in the right ventricle In 14 of the 34 cases in which the pressure in the right ventricle was increased he found notches in the descending leg of the I depression and or in the ascending leg of the J wave sometimes combined with a high H peak No attempt was made to determine systematically whether there was any relationship between the ballistocardiographic abnormalities and the size of the shunt No easily characterized BCG pattern could be demonstrated for the atrial septal defect

Jonnart[2] investigated 3 cases with the ultralow frequency method and found no abnormalities in the BCG No mention is made of whether the displacement tracing or its derivatives were studied

In an earlier study using the ultralow frequency method according to Burger[3] and analyzing the results according to the empirical method used at that time we found abnormalities in the BCG in 6 of 10 cases. We described these changes as a lowering of the J depression of the displacement tracing with corresponding deviations in the I and the I depressions of the velocity and acceleration tracings respectively With this method no relationship was found between the deviations in the BCG and the size of the shunt

A new study of the BCG in atrial septal defect was based on Noordergraaf s theory concerning the genesis of the BCG under normal conditions [5,6] In particular use was made of the contribution of the lesser circulation as calculated by this author

One of the objectives of this study was to investigate whether there is a relationship between the deviations found in the BCG and the size of the shunt.

Theoretical considerations

Noordergraaf based his theory on the principle that the total change in the mass distribution in the body during the cardiac cycle may be described as the displacement of the internal center of gravity In other words the displacement of the internal center of gravity can be calculated as the algebraic sum of all the separate mass displacements occurring in the cardiovascular

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system during the cardiac cycle. The displacement BCG is then the curve of the displacement of the body in the opposite direction.

To enable calculation of the BCG under normal conditions, the contribution of each cardiovascular phenomenon had to be calculated separately. In these calculations all mass displacements were related to one arbitrarily chosen reference plane.

The entire arterial system, including the pulmonary arteries, was considered for this purpose as being divided into a number of segments, permitting the contribution to be calculated per segment. The size of one such segmental contribution at a given moment in the cardiac cycle is determined by the product of the excess mass of this segment above the end-diastolic level and the distance to the plane of reference; the excess mass at a given moment is proportional to the volume of the segment in question and the rise in pressure in the segment at that moment.*

To determine the contribution formed by the filling and emptying of the heart and the associated heart motion, which for the sake of brevity may be called the central contribution, the same system was followed in principle. It was assumed that the right and left heart make equal contributions.

All contributions were aligned in time and totaled for the construction of the displacement BCG under normal conditions. Velocity and acceleration curves could be easily derived by differentiating the displacement curve once and twice, respectively, in relation to time.

The contribution of the venous system could not be calculated as yet.

In the hemodynamic sense, atrial septal defect is characterized by an increase in the flow in the lesser circulation. From the ballistocardiographic point of view this means not only an increase in the excess mass above the end-diastolic level in the pulmonary arteries, but also an increase in the mass change in the right heart and an increase in the related displacement of the heart.

In order to predict the changes in the shape of the curve of the total BCG as calculated by Noordergraaf and his co-workers for a progressive increase in the flow in the lesser circulation, the contribution formed by the excess mass in the pulmonary arteries under normal conditions was added 1, 3, and 5 times to the normal curve. To include the influence of the central component on the shape of the BCG as well, the central contribution was added to the resulting curve a proportional number of times (1/2, 1 1/2, and 2 1/2) because atrial septal defect involves extra loading of only the right heart, and for his calculations Noordergraaf had assumed that the right and left heart make the same contribution.

In this way, theoretical curves were constructed for the displacement, velocity, and the acceleration (Figs. 1, 2, and 3).

An increase in the excess mass in the pulmonary arteries and the right heart is expressed in the predicted displacement curve (Fig. 1) as an increase in the height of the atrial G peak and increased depth and width of the J depression, whereas the M wave is appreciably smaller as a result of a decrease in height and width.

The predicted velocity curve (Fig. 2) shows corresponding changes. Following the current style in nomenclature,[4] there is now, however, a broadening and deepening of the I depression or, in other words, a surface increase. On the contrary, the J wave does not differ much in height and width.

The predicted acceleration curve of course shows the same changes (Fig. 3), but because of the differentiation the picture is much less distinct as compared to the velocity and displacement curves, and an increase in the amplitude of almost all the waves predominates.

With an increase in the excess mass in the lesser circulation, an increase can be expected in all the quantities of the BCC in the N or MN and MN amplitudes as far as the early diastolic phase is concerned.

*Since the density of the blood is taken as 1, mass and volume are numerically equal and mass may be substituted for volume. The complete equation derived by Noordergraaf is $\Delta V = 3V \frac{(n+1)^2}{E(2n+1)} \Delta P$, where V is the volume of the segment, ΔV is the volume of the blood above the end-diastolic volume level in the segment, n is the ratio between the internal radius and the thickness of the wall of the artery, E is the modulus of elasticity (Young's modulus), and ΔP is the increase in the internal pressure above the end-diastolic level.

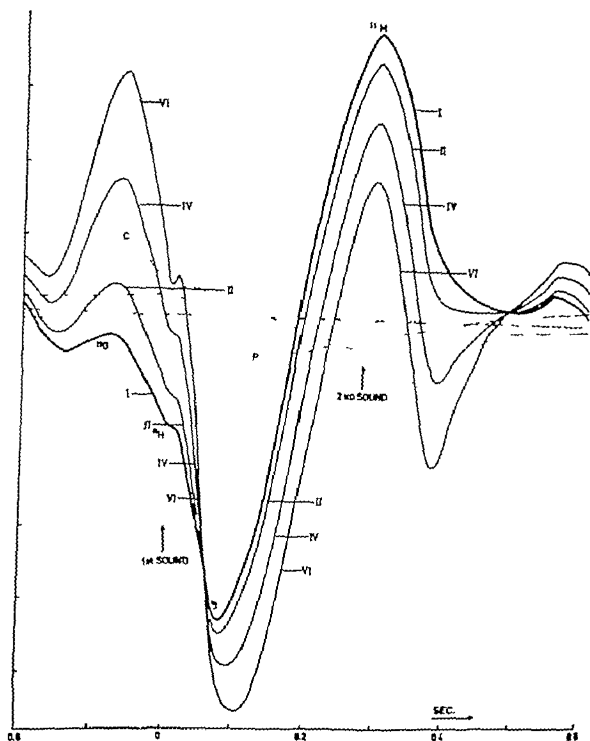


Fig. 1. Modifications in the shape of the displacement BCG calculated by Noordergraaf (*heavy line I*) after an increase in the excess mass in the lesser circulation. Line *P* is the contribution of the pulmonary arteries, line *C* is the total contribution formed by the filling and emptying of the heart and the associated heart motion calculated for normal conditions. The fine lines *II*, *IV*, and *VI* were constructed by the addition to line *I* of quantities representing 1, 3, and 5 times the amplitude of line *P* and ½, 1½, and 2½ times the amplitude of line *C*; these amplitudes are related to the horizontal dashed line representing the arbitrarily chosen plane of reference. "G, "H, etc. indicate the waves and depressions of the displacement BCG according to the usual nomenclature.

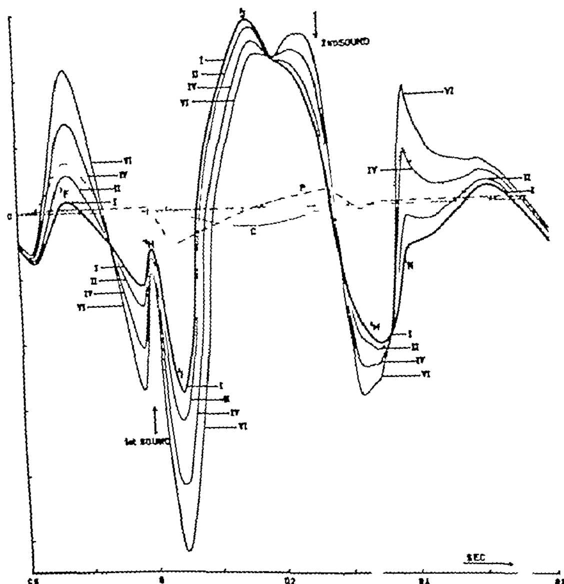


Fig. 2. Modifications in the shape of the velocity BCG calculated by Noordergraaf after an increase in the excess mass in the lesser circulation. The zero line (dashed) is indicated by 0, the other symbols are as in Fig. 1. 'F, G, etc., indicate the waves and depressions of the velocity BCG according to the usual nomenclature.

If we restrict ourselves to the velocity curve and plot the quotient

$$\frac{\text{area I depression}}{\text{area J wave}}$$

against the increase in the excess mass in the lesser circulation (Fig. 4) this quotient is found to increase with the increase in the excess mass. This quotient can thus be used to characterize the velocity curve in atrial septal defect.

It is true that an increase in the area of the J depression in relation to the "M" wave is also to be expected in the displacement curve but measurements of the displacement curve are complicated by the fact that in the physical sense there is no zero line. For this reason the velocity curve was used to describe the qualitative changes in the BCG with different degrees of increase in the flow in the lesser circulation in atrial septal defect.

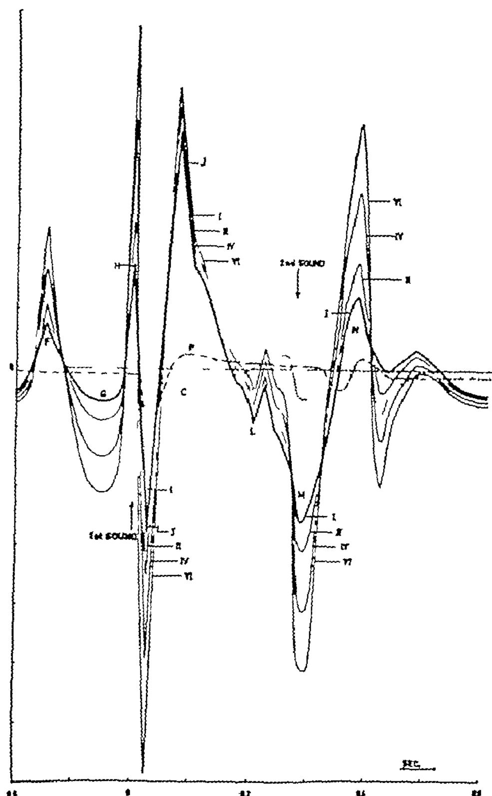


Fig. 3. Modifications in the shape of the acceleration BCG calculated by Noordergraaf after an increase in the excess mass in the lower circulation. The zero line (*dashed*) is indicated by O; the other symbols are as in Fig. 1. F, G, etc., indicate the waves and depressions of the acceleration BCG according to the usual nomenclature.

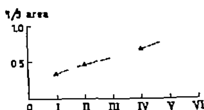


Fig. 4. Predicted changes in the 'I/'J area quotient of the velocity tracing with increasing excess mass in the lesser circulation. The Roman numerals indicate the multiplication factor of excess mass in the lesser circulation. It was assumed that the excess mass in the systemic circulation did not change. The data derive from the tracings shown in Fig. 2. For normal conditions (corresponding with I) the quotient was found to be 0.36.

Method and material

The ballistocardiograph was the same as that used in previous investigations.[2] The transducer consisted of an accelerometer and the velocity tracing was obtained by means of an integrating electrical circuit. Calibration was carried out according to Schmidt[7]: a force of 70 grams is allowed to act periodically with a frequency of about 3 cycles per second on the ballistocardiograph that is loaded so that the total dead weight is 70 kilograms.

A BCG was obtained under basal conditions in 34 patients with uncomplicated atrial septal defect who varied in age from 7 to 52 years; in 6 cases a BCG was recorded both before and after closure of the defect. The systemic and pulmonary flows were calculated according to the Fick method.[8] The BCG could not be obtained concurrently with these determinations of flow.

From the velocity tracing the ratio between the area of the I depression and the area of the J wave was calculated, both areas being measured in relation to the zero line. This base line was determined planimetrically so that the total area inscribed during one heart cycle above this line equaled the same area below this line.

Results

In 31 of the 34 cases in which a shunt could be demonstrated and its size calculated, an increase in the area of the I depression with respect to the J wave was found in the BCG. For the other 3 cases,

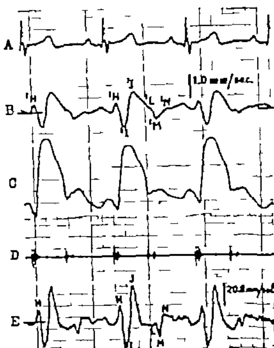


Fig. 5. BCG in atrial septal defect with a small shunt. Pulmonary flow 10.7 L. per minute, systemic flow 9.7 L. per minute. *A*, ECG Lead II. *B*, Velocity curve with zero line; letters as in Fig. 2. *C*, External carotid artery tracing. *D*, Phonocardiogram. *E*, Acceleration curve with zero line; letters as in Fig. 2.

only a slight or moderate increase in the pulmonary flow was calculated; the quotient fell within the norm in these cases.

The BCG of such a patient with a very small shunt is shown in Fig. 5. The velocity and acceleration tracings cannot be distinguished from normal tracings. The highest point of the 'H wave in the velocity tracing practically coincides with the beginning of the external carotid artery tracing; as a result of the differentiation the synchronism of the latter point with the peak of the H wave of the acceleration tracing is even more striking. This point of the acceleration tracing indicates the beginning of the ejection. The 'H and H waves are preceded respectively by a flat 'F 'G segment and F-G segment corresponding to the atrial activity. After

*For the quotient $\frac{\text{area I depression}}{\text{area J wave}}$ an average value of 0.3[illegible] was found in our material comprising normal young subjects. Calculated on the basis of data taken from [illegible] this value was 0.3[illegible]

the H and H waves, the I and I depressions are inscribed respectively followed in turn by the J and J waves

The velocity tracing of normal young subjects shows the inflection point L on the descending leg of the J wave corresponding to the L point of the acceleration tracing These *inflection points may coincide with the first or the second part of the second sound In this case there is synchronism with the second or pulmonary part of the second sound This point represents the end of the ejection*

The early diastolic part of the velocity tracing shows a distinct drop below the zero line This is followed by a rather slow rise in the curve These two phases together form the MN segment The corresponding part of the acceleration tracing is the MN segment With respect to the time relationship this portion of the tracing is recorded during the rapid filling phase of the ventricles. A clearly developed early diastolic portion with the configuration described above is characteristic of the BCG in normal young subjects.

There is also no convincing quantitative difference with respect to the normal tracing, the quotient of the area of the I depression and J wave still lies within the norm

With a pronounced increase in the pulmonary flow on the contrary there is a radical change in the shape of the velocity tracing (Fig 6 curve *B*) There is an increase in the atrial wave. With respect to the zero line the I depression is markedly lower and wider whereas the area of the J wave shows no distinct increase The maximum amplitude of the curve (IJ) has thus increased but this increase is effected by the increase in the I depression As a result the area quotient in this case is 1 4 The early diastolic portion does not reach the zero line

The acceleration tracing also shows an increase in atrial activity (Fig 6 curve *F*) Although there is an increase in the amplitude (IJ) of the curve as well in contrast to the velocity curve the change in shape with respect to the normal curve is not striking

That these changes in the shape of the BCG *must* depend upon an increase in the flow in the lesser circulation is evident

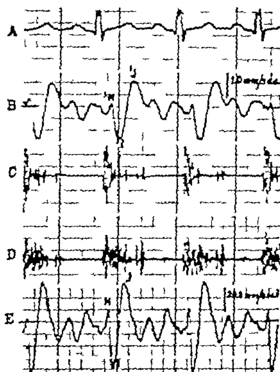


Fig 4 BCG in atrial septal defect with large shunt Pulmonary flow 22 3 L per minute systemic flow 3 7 L per minute *A* ECG Lead II *B* Velocity curve with zero line letters as in Fig 3 *C* and *D* Low frequency and high-frequency phonocardiograms. *E*, Acceleration curve with zero line letters as in Fig 3

from the postoperative tracings. The amplitude of the velocity tracing (Fig 7 curve *B*) is half as large as the amplitude before the operation and the area of the I depression is now only a fraction of that of the J wave In addition an easily distinguished early diastolic M depression is now present The ascending leg of this depression is, as it were intercepted by the atrial activity of the next heart cycle This is caused by the high heart frequency and the prolongation of the P R interval

The amplitude (IJ) of the acceleration tracing (Fig 7 curve *E*) is reduced to a third as compared with the preoperative tracing

In Fig 8 the I J area quotient is plotted against the ratio of pulmonary to systemic flow for 36 patients. In 2 cases the suspicion of a shunt at the atrial level raised by the routine clinical examination was not confirmed by catheterization of the heart. In these cases, as in the 3 cases al

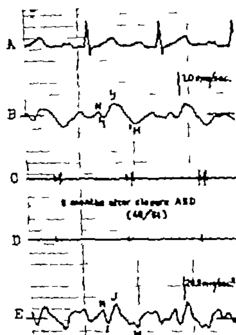


Fig. 7. BCG of the patient shown in Fig. 6, nine months after closure of the defect. *A*, ECG Lead *II*. *B*, Velocity curve with zero line; letters as in Fig. 2. *C* and *D*, Phonocardiograms. *E*, Acceleration curve with zero line; letters as in Fig. 3.

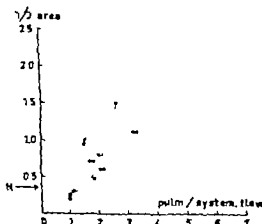


Fig. 8. I/J area quotient calculated from the velocity curve plotted against the ratio of pulmonary to systemic flow in atrial septal defect. The open dots indicate cases with a small shunt or a shunt too small to be calculated. The solid dots indicate the remaining cases. N is the normal value of the area quotient. The dashed line indicates the mean relation between the measured quantities the predicted points (taken from Fig. 4) assuming quadratic relationship between increase in pulmonary flow and increase in excess mass.

ready mentioned with a slight or moderate increase in the pulmonary flow the I J area quotient fell within the norm. For the other cases it is clear that in general an increase in the pulmonary flow was accompanied by an increase in the area of the I depression with respect to the area of the J wave. When the pulmonary flow is doubled or more than doubled these areas become equal or the area of the I depression surpasses that of the J wave. The latter was found in more than half of the cases.

Discussion

The aim of the investigation was to test whether the changes in the shape of the BCG expected on the basis of Noordergraaf's calculations for increase in excess mass in the lesser circulation would correspond to the actual changes found in cases of atrial septal defect. A qualitatively limiting factor in the construction of the curves lies in the fact that Noordergraaf was unable to calculate the contribution of the venous return to the BCG under normal conditions. As a result the hemodynamics of the caval veins at the beginning of diastole as influenced by the atrial septal defect are not expressed in the predicted curves. In all probability this explains the absence in the clinical curves of the theoretically expectable early-diastolic deep M and M depressions (Figs. 2 and 3). Because of the lack of exact data, we will exclude this portion of the curve from consideration.

In agreement with theoretical expectation, the acceleration curve in atrial septal defect was found to undergo no marked changes.

The observed modifications in the systolic portion of the velocity tracing show good qualitative agreement with expectation with an increase in the shunt there is an increase in the area of the I depression. In this connection it is striking that, with the exception of a small number of cases even in cases in which the flow in the pulmonary circulation is not yet doubled the area of the I depression is nevertheless, already far above the norm. As a result in the large majority of cases for which a doubling or greater increase in the flow of the pulmonary circulation is

calculated an I/J area quotient of 1 or more was found (Fig. 8).

Closer study of the deviations (Fig. 8) reveals a rather large spread of the points. Here it must be kept in mind that the material was biological and included patients who were over 40 years old. It is known that above this age the BCG often shows modifications without the presence of demonstrable lesions.[9] In addition, the determinations of flow and the BCG were not obtained simultaneously; furthermore, the standard deviation for the determinations of flow according to Fick is large.[8]

In 3 cases in which there was greatly increased flow in the lesser circulation, widely deviating values were found for the I/J area quotient. In these cases there was a marked dilatation of the pulmonary artery. It is probable that in such conditions there are also changes in the wall of the vessels which, besides the increase in pulmonary flow, radically affect the velocity of the pulse wave and, as a result, the I/J area quotient as well.

In the quantitative sense, the expected and the clinically established changes in the velocity tracing may not be directly compared. For the predicted curve the I/J area quotient is plotted against an increasing excess mass in the pulmonary circulation (Fig. 4), but in the clinical cases this quotient is plotted against an increase in pulmonary flow (Fig. 8). These graphs would only be directly comparable if there were a linear relationship between increase in pulmonary flow and increase in excess mass. However, the relationship between these two factors is unknown. Perhaps this relationship may be approached via a closer examination of the equation derived by Noordergraaf for the ballistocardiographic effect of a single arterial segment (see footnote, page 187). Although flow does not appear in this equation, it is clear, nevertheless, that in elastic vessels an increase in flow implies an increase in excess mass. It is quite conceivable that a linear increase in flow could produce a quadratic increase in the excess mass, since there would be a resulting increase in both the volume already present in the pulmonary circulation and at the end-diastolic level (V in the equation) and in the change in pressure in the pulmonary arteries (ΔP in the equation). The view of a quadratic relationship has also been put forward by Starr.[10,11]

Because a quadratic relationship is probable, therefore, the theoretically derived points in Fig. 4 have been corrected in this sense, and the new values included in Fig. 8. These corrected points all fall in the distribution range of the large majority of points calculated from the velocity BCG of the clinical cases.

To summarize, it may be stated that in uncomplicated atrial septal defect both the systolic and the early-diastolic phases of the BCG undergo a marked change in shape. Noordergraaf's concept and the application of the calculations based on it are extremely useful for a new interpretation of the systolic phase of the clinical BCG. The discrepancy between the predicted and the recorded early-diastolic phase of the BCG must in all probability be attributed, as has already been said, to the impossibility of expressing the influence of the venous return in the predicted curves. Clearly, a comprehensive interpretation—including the diastolic phase—requires the calculation of the venous contribution under normal conditions.

Summary

The previously described changes in the ultralow frequency BCG that accompany atrial septal defect have been reinvestigated in the light of Noordergraaf's considerations concerning the genesis of the BCG and his prediction of the BCG under normal conditions. The calculated contribution of the lesser circulation was used to construct a series of curves reflecting as closely as possible the situation resulting from successive increases in the pulmonary flow.

The modifications in the predicted and the clinical curves show very good agreement. The most striking finding was that with an increase in the pulmonary flow there was an absolute increase in the area of the I depression of the velocity curve. The changes found for the acceleration curve are not easily characterized.

It is considered to be possible that with an increase in the pulmonary flow the change in volume above the end-diastolic

level in the lesser circulation increases not linearly but quadratically

Noordergraaf's theory has proved to open new ways for the interpretation of the clinical ballistocardiogram.

We are greatly indebted to Professor H. A. Snellen for his encouragement and critical reading of this paper We also wish to thank Mr J J Magdelijns for preparing the drawings.

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The effects of digoxin on the electrocardiogram after strenuous exercise in normal men

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The most important effects of digitalis on the resting electrocardiogram are displacement of the S-T and reduction of the height of the T wave. These are dependent to some degree on the dose and duration of digitalization[1,2] and are exaggerated by cardiac disease.[3] They are often accompanied by a decrease in the relative Q-T interval, especially apparent at slow heart rates.[3,4] These changes are believed to be due to quickening of the repolarization process in ventricular muscle.[4,5]

Mild and moderate exercise also accentuate these ST-T changes. Zwillinger[6] and Liebow[7] both reported ST-T changes in the electrocardiograms of digitalized normal subjects after mild exercise. These changes have since been commonly observed to increase with increasing severity of effort.

Effort, in contrast to digitalis, produces a relative prolongation of electrical systole.[8] Mild and moderate exercise produce diminution in T waves, similar to that with digitalis. Strenuous anaerobic effort, unlike digitalis, is often followed by large increases in the height of the T wave, particularly in untrained subjects.[3] This increase is prevented by atropine[3] and thought to be due possibly to increased vagal activity[3] or myocardial hypoxia.[9]

The present study was undertaken (a) to determine the electrocardiographic effects of digoxin during and after strenuous exercise in normal subjects, (b) to ascertain whether these effects are fortuitous or whether they are reproducible, and (c) to ascertain whether they can be modified by atropine. Atropine exerts effects on the resting electrocardiogram of digitalized subjects. Conflicting reports claim both an aggravating and an attenuating effect on the ST-T changes induced by digitalis.[9,10]

Materials and methods

Nine volunteers participated in the experiment. All were males; they ranged in age from 20 to 33 years and were in good health. Table I shows their age, height, and weight. Five exercise tests were performed by each subject as shown in *Table II*. Eight subjects were on digoxin for at least 1 month prior to test 2. One subject who was rapidly digitalized performed exercise tests 6 hours and 1 week after the first dose of digoxin. When possible, at least 3 days elapsed between each test in order to minimize the effects of training.

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Table I. Pertinent data on 9 normal males

Subjects	*Age (yr.)*	*Weight (pounds)*	*Height (inches)*
1	30	176	68
2	28	142	69
3	20	153	71
4	.3	156	64
5	25	158	72
6	27	1 4	70
7	25	154	68
8	33	158	71
9	31	164	67

Table II. Exercise tests

Test number	*Medications*	*Number of subjects*	*Days between each test*
1	None	9	2* 31
2	Digoxin	9*	1 7
3	Digoxin	8	2-9
4	Digoxin, atropine	9	33-67
5	None	8	—

*One subject exercised 6 hours after 1.5 mg. dose of digoxin intramuscularly.

Digoxin was taken orally 1 mg. daily for 5 days then 0.5 mg daily. One subject was given 1.5 mg. of digoxin intramuscularly as an initial digitalizing dose. Atropine, 2.4 mg. was administered intravenously 10 minutes before test 4.

Each test was preceded and followed by the recording of a resting 12 lead electrocardiogram. There was a 10-minute control period in the upright position. The subjects then walked on a treadmill at a 5-degree slope for three periods of 3 minutes each and one period of 6 minutes at 3, 4.5, 6 and 7.5 kilometers per hour (Km. hr.) respectively with intervening rest periods of 3 minutes each. Ambient temperature was between 18 and 20°C and relative humidity was between 50 and 60 per cent.

Heart rate was monitored every 30 seconds by a heart rate meter* or pulse totalizer. Electrocardiographic records were taken before, during, and after each exercise load and at 2 minute intervals during recovery. A Sanborn four-channel direct writing recorder was used.

A modification of a previously described electrocardiographic lead system[12] was employed in taking three simultaneous bipolar leads: ensiform process-right ear (CH_{5-8}), V_2-right ear (CH_2) and V_4-right ear (CH_4). Modified saline bridge electrodes of a type previously described gave records of good quality during exercise.[12,13]

Tests were carried out between 11:00 A.M. and 4:00 P.M. In order to minimize extraneous effects on exercise electrocardiograms, the subjects refrained from smoking and severe exercise and ate a low fat diet in the preceding 12 hours. Two to 3 hours prior to testing, the subjects ate a standard fat free meal of approximately 600 calories.[14] The level of physical activity (subjectively reported) and body weight remained constant throughout the experimental period.

Electrocardiographic analysis. In the resting electrocardiograms P-R and Q-T intervals were taken from Lead II. S-T and T wave changes were determined particularly for Leads V_4-V_6 by three independent observers.

In the exercise electrocardiograms, QRS and T amplitudes were taken from Leads CH_4. Because of the poor demarcation of the end of the T wave at the rapid heart rates, the Q-aT (Q to the apex of T wave) of Lead CH_1 instead of Q-T was used. This was valid since the Q-aT expressed as a percentage of the Q-T is relatively stable (68 to 84 per cent). Furthermore the Q-aT shows the same dependence on heart rates as does the Q-T.[16] Although the duration of the T wave shortens with increasing heart rate, shortening of the S-T segment is the major factor contributing to the reduced Q-T interval which accompanies tachycardia.[17] Q-T intervals in the resting electrocardiograms and Q-aT intervals in the exercise electrocardiograms were calculated from Bazett's formula.[8]

In the exercise electrocardiogram S-T and T wave amplitudes were measured from a line connecting the end of the P-R interval in two sequential comp

*Constructed by the Department of Medical Electronics, Royal Melbourne Hospital.

S-T segment heights were measured just before the onset of the T wave in order to minimize effects of j point depression which occurred with tachycardia in some instances. When this point was in doubt, a point was used which was 25 to 30 per cent of the distance between the onset of the two bordering QRS complexes.

Student's *t* test was used for statistical analysis.

Results

Exercise electrocardiograms prior to digoxin. Changes in T wave amplitude during and after each work load are shown by solid dots in Fig. 1. Although the pattern of T wave change during and after exercise varied from subject to subject, it was generally consistent for each subject from 3 to 6 Km. hr. There was no marked change in T wave heights at these levels of effort. In all but 1 of the subjects (Subject 8) T waves reached their maximum during the first 2 minutes after 7.5 Km./hr. These increases were often relatively abrupt and ranged from 2 to 5 mm. above the T waves during the previous level of exercise. These increases were often 5 to 10 times greater than that of their respective R waves. The greatest increases were constantly found in Leads $CH_{1,4}$ and CH_4 and least in Lead CH_6.

The measurement of T wave heights during strenuous exercise was reliable. Fig. 2 shows that although the QRS amplitude varies widely (from 24 to 34 mm.) the T waves remain relatively stable (between 8 and 9 mm.). Instability of the QRS is apparently a function of the saline bridge electrodes which cause respiratory interference occurring during strenuous exercise to be manifest as a

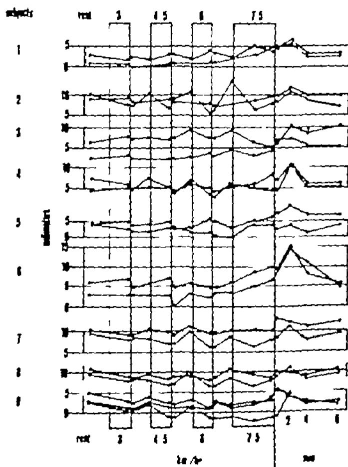


Fig. 1. T wave amplitude during and after exercise in 9 normal subjects. *Solid dots:* No digoxin. *Open dots:* Digoxin. In Subject 9 the crosses (X) indicate early portion of the T wave with digoxin.

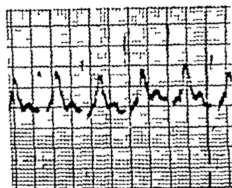


Fig. 2. Electrocardiogram (Lead CH) taken during strenuous exercise. The T-wave amplitude is stable. The QRS amplitude changes significantly with respiration.

variation in QRS height rather than as a wandering base line in the electrocardiogram.

Exercise electrocardiograms with digoxin. After digitalization, increasing downward displacement of the S-T segment occurred during strenuous exercise in 4 subjects. These subjects had previously shown minor ST-T changes in their resting electrocardiograms which could only be detected when compared with their electrocardiograms recorded before digoxin. Fig. 3 shows the progressive nature of the S-T segment depression immediately after exercise. These changes remained for at least 2 minutes after the cessation of the 7.5 Km. hr. work load. Repeat testing produced similar changes in all of the subjects. Likewise those in whom no S-T changes appeared with exercise gave repeatedly a negative result. After acute digitalization in 1 subject S-T depression was not nearly so severe as after 1 week of digoxin.

Fig. 1 shows T wave heights after digitalization. From 3 to 6 Km. hr. the exercise T waves remained upright in 8 subjects and although smaller generally followed the same trends as the exercise T waves prior to digitalization. With digoxin major increases in T-wave amplitude (greater than 2 mm.) occurred in 4 subjects (Subjects 2, 4, 7 and 8). Invariably these increases were greatest 2 to 3 minutes after the previous exercise. Major decreases occurred during exercise in these same 4 subjects. After 7.5 Km. hr., 8 subjects showed a further rise in T wave amplitude. In all except Subjects 3 and 5 T wave heights were similar before and after digitalization. One subject (9) had marked inversion of all but the terminal portion of the T wave at all levels of exercise. This reverted 2 minutes after 7.5 Km. hr. (Fig. 3).

Although the Q-aT interval decreased the Q-aT interval gradually increased with exercise both with and without digoxin. The mean Q-aT increased during each exercise period. It ranged from 0.300 second at rest to 0.325 second during 7.5 Km. hr. prior to digitalization, and from 0.300 to 0.340 second at rest and during 7.5 Km. hr. respectively after digitalization. These increases were both statistically significant (p = .02 or less) and did not correlate with changes in the S-T segment or T waves. After 2 minutes of recovery the Q-aT had returned to control levels. In a comparison of the Q-aT intervals before and during digitalization there was no statistical difference at any level of exercise. Thus the Q-aT although affected by exercise was not affected by digitalization. Likewise the exercise Q-aT intervals were not significantly different in a comparison of those subjects who did and those who did not have S-T changes in the exercise electrocardiogram with digoxin.

Exercise electrocardiograms in digitalized subjects with atropine. Chest head electrocardiograms taken at rest 10 minutes after atropine revealed slight S-T depression in 2 of the 4 subjects who had progressive S-T depression during exercise while on digoxin. In the other 7 there was no change in the S-T from that recorded prior to atropine.

In the total group T wave lowering occurred at rest after atropine in 7 subjects, inversion occurred in 1 and there was no change in 1. Table III shows heart rates during 4.5 and 7.5 Km. hr. before and after digitalization and with atropine. The presence of exercise S-T depression in the 4 subjects did not correlate with the relative physical fitness of the subjects as determined by their heart rates at each of the work loads. Heart rates during exercise prior to and during the administration of digoxin were not statistically different.

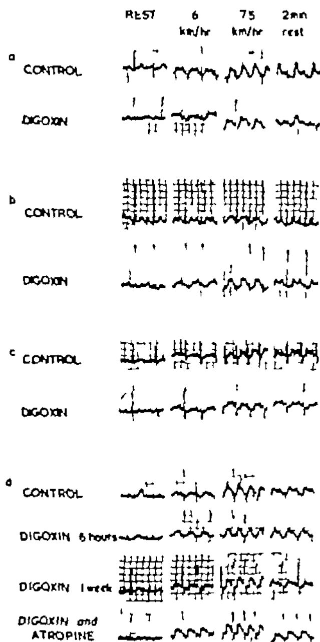


Fig. 3. Electrocardiogram (Lead CH) immediately after moderate and severe exercise and after 2 minutes of rest in 4 subjects who showed S-T changes during digitalization (Subjects 1, 3, 5, and 9). In Subject 9 S-T depression paralleled the duration of digitalization. Atropine produced little change in S-T depression.

Digoxin-induced S-T depression did not correlate with the degree of tachycardia induced by atropine which was particularly apparent at milder work loads (4.5 Km./hr.). Although exercise S-T depression was generally greater after atropine in Subjects 5 and 9, it did not increase in the other 2 subjects.

Resting 12-lead electrocardiograms. In the 4 subjects with digoxin-induced exercise S-T changes, the resting electrocardiograms showed minor S-T depression and decrease in T wave heights (Table III). An increase in the resting P-R interval greater than 0.2 second and a decrease in the Q-T, however, were inconsistent findings which did not coincide with changes in the digoxin exercise tests.

Table III. Heart rate and electrocardiographic response to moderate and strenuous exercise in digitalized subjects with and without atropine

Subject	Heart rate during third minute at 4.5 Km./hr			Heart rate during sixth minute at 7.5 Km./h			Digitalis effect		
							12-lead ECG		Progressive S-T depression with increasing exercise
	Control	Digoxin	Digoxin atropine	Control	Digoxin	Digoxin atropine	ST	T	
1	109	112	126	166	144	156	+	0	+
2.	119	116	133	168	165	168	0	0	0
3	120	118	148	154	146	163	+	+	+
4	126	112	134	180	174	176	0	0	0
5	108	108	134	164	158	168	+	+	+
6.	114	105	148	16_	157	1_8	0	0	0
7	106	110	134	132	143	161	0	0	0
8.	112	102	1_3	150	150	155	0	0	0
9	112	110	131	154	161	169	+	+	+
Mean	114	111 N.S.	135 p .001	159	156 N.S.	16_ N.S.			

N.S. = No significant difference from control heart rates.

Discussion

ST-T wave changes with exercise without digoxin. An increase in the height of the T wave occurred in 8 subjects after strenuous exercise. This was not associated directly with the exercise heart rate inasmuch as it was most pronounced 1 to 2 minutes after exercise at a time when the heart rate had diminished. Furthermore, in these subjects, after lighter work loads at roughtly comparable heart rates, large T waves and relatively smaller R waves were not observed.

During exercise it was difficult to determine whether an increase in the T wave was in fact real. It may have been caused by an altered base line due to depressed P-T waves or by superimposition of the U wave on the T. Two minutes after rest however the P-R segment was relatively horizontal. The heart rate had slowed somewhat so that if significant U waves were present, one would expect to see them. Thus, the changes observed 2 minutes after exercise represented a true increase in the T wave.

Kahn and Simonson[8] found that postexercise elevation of the T wave occurred only after anaerobic effort. Determinations* of lactic acid in serum from the forearm that were made at the work loads used in this study in our laboratory did not rise greatly until the 7.5 Km./hr. level, after which a pronounced increase (greater than 50 mg. per cent) was found. Furthermore, the actual expenditure of energy is not linearly proportional to the speed of the treadmill but is disproportionately more strenuous than at lighter work loads.[19] To insure the production of a sizable oxygen debt, 6 instead of 3 minutes of exercise was employed at 7.5 Km./hr.

Elevation of the T wave after anaerobic exercise occurred in 8 subjects in this study on two occasions, 3 months apart. The reproducibility of these electrocardiographic changes make the exercise electrocardiogram a good parameter with which to compare the effects of digoxin.

Exercise and digoxin. Several authors have described stages of increasing digitalis effect in the resting electrocardiogram which correspond to increasing dosage and duration of digitalis administration in normal subjects.[4] Lepeschkin[9] describes four such stages, during which the

*Enzyme method, lacta, and ... by C. F. Boehringer and Soehne GmbH, Mannheim, Germany.

S-T segment and upstroke of the T wave become increasingly depressed whereas terminal T wave amplitudes remain relatively unchanged. These changes have been shown to appear 1 to 15 minutes after intravenous digitoxin and to last for 3 to 4 days. In another study they have been demonstrated to increase in severity over a period of weeks.[1] The changes found in the present study after increasing effort are identical to the stages described at rest. Subject 9 especially shows the advanced stages of S-T segment and T wave upstroke depression (Figs. 1 and 3). Similarly, terminal T waves have been preserved with increased heights, as in the predigitalization exercise electrocardiogram. The only difference between resting and exercise digoxin effects was the relative duration of electrical systole (as measured by the Q-aT interval). It lengthened instead of shortening as occurs with the administration of digitalis at rest. With both exercise and digitalis, however, the uncorrected Q-T interval diminished.

S-T changes due to digoxin were reproducible in the 4 subjects who responded to the drug. Likewise such changes were constantly absent in the other 5 subjects. This means that digoxin exercise effect was not solely dose dependent, but in the therapeutic range was subject to individual variation.

Factors which determine the electrocardiographic response to digoxin in the normal subjects are unknown. Atropine has been reported to accentuate digitalis-induced T wave diminution in the resting electrocardiogram.[2] In this study, 8 digitalized subjects showed T wave flattening 10 minutes after intravenous atropine. It has also been reported to cause a partial or total disappearance of ST-T changes in the resting electrocardiogram of digitalized subjects.[19]

This conflict is of interest, inasmuch as increased vagal tone has been thought to be a possible mechanism whereby digitalis causes ST-T changes.

The present study demonstrates that during exercise, at least, autonomic effects do not seem to play an important role. Atropine neither altered the exercise electrocardiographic changes with digoxin nor caused such changes to appear in subjects who previously did not exhibit them.

If digoxin causes ST-T changes by producing myocardial hypoxia, and if tall T waves that develop after severe effort are due to general myocardial ischemia, as postulated by Kahn and Simonson,[4] then with digoxin tall T waves might be expected to appear after less severe levels of exercise. This did not occur in the present study.

Employing the concept of ventricular gradient of Wilson, Ashman[19] believes that digitalis-induced ST-T changes are due to a reduction in the ventricular gradient so that the time courses of depolarization and repolarization of the cardiac regions become almost equalized. Since rapid heart rate and digitalis both tend to diminish the ventricular gradient,[11] their cumulative effect might exaggerate electrocardiographic ST-T changes.

Finally, it is possible that electrocardiographic digoxin effect is a function of altered myocardial electrolyte relationships, with a relative deficiency of intracellular potassium. Tachycardia and increased force of contraction[12] which occur during effort may also lead to a relative deficiency of intracellular potassium. In such a situation the superimposed effect of effort would tend to accentuate the electrocardiographic effects of digitalis at rest.

Summary

Nine normal subjects each performed a series of progressive exercise tests before and after long-term digitalization.

Predigitalization exercise electrocardiograms showed a marked increase in the T waves 2 minutes after strenuous effort and a progressive increase in the relative Q-aT interval.

With digoxin, progressive S-T depression occurred in the exercise electrocardiograms of 4 subjects. This did not prevent elevation of the T wave after effort, nor did it alter the increased corrected Q-aT interval. Exercise S-T depression occurred only in those subjects whose resting electrocardiograms showed digoxin-induced S-T depression. Its appearance was not fortui

tous but was reproducible in effort tests of all of the 4 subjects and was consistently absent in the other 5 subjects.

Atropine did not significantly alter the effect of digoxin on the exercise electrocardiogram. This suggests that the effect is not mediated via the autonomic nervous system.

Progressive transient digitalis effect with exercise resembles in many respects the progressive effects which appear after the administration of digitalis at rest. Increasing effort may help to produce metabolic, *electrolyte or electrical conditions* which enhance the electrocardiographic effects of digitalis at rest.

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The effects of digoxin on the electrocardiogram after strenuous exercise in normal men

II Effect of potassium chloride with and without insulin on the exercise electrocardiogram of digitalized subjects

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It has been suggested that digitalis-induced ST T changes in the resting electrocardiogram are related to those which appear during exercise[1] The latter may represent an enhancement of resting digitalis-induced ST T changes via a mechanism which promotes a further rapid depletion of intracellular potassium

This study was carried out to ascertain whether digitalis-induced changes in the exercise electrocardiogram could be reversed by potassium either with or without insulin

Materials and methods

Two chronically digitalized normal males who consistently developed progressive ST T changes in their exercise electrocardiograms participated in this study (*Subjects 1 and 9*)[1] They underwent a standard exercise test[1] on two occasions as previously described For 2 days prior to the first test they were given oral liquid potassium chloride 12 to 15 Gm per day and they ate a 600-calorie carbohydrate meal 2 hours before the test One and one-half hours before the second test regular insulin 20 units, was injected subcutaneously This was followed by the ingestion of a 600-calorie carbohydrate meal with 4 or 5 Gm of liquid potassium chloride added Electrocardiograms were recorded at appropriate intervals immediately after exercise and at rest[1]

Results

The comparative effects of potassium with and without insulin on the exercise electrocardiogram (Lead CH_4) are shown in Figs. 1 and 2 It is apparent that in Subject 1 (Fig 1) the slight but consistent lowering of the S-T segment was unchanged by potassium alone but was abolished by the addition of insulin Moreover T waves were higher after potassium with insulin than with digoxin alone at all levels of effort

Subject 9 who showed more advanced ST T changes with digoxin responded in a similar manner (Fig 2) Potassium alone did not alter the digoxin induced ST T changes in the exercise electrocardiogram

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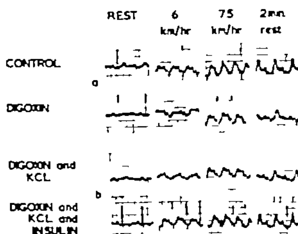


Fig. 1. Electrocardiograms of a normal male (Subject 1) immediately after moderate and severe effort and after 2 minutes of rest.

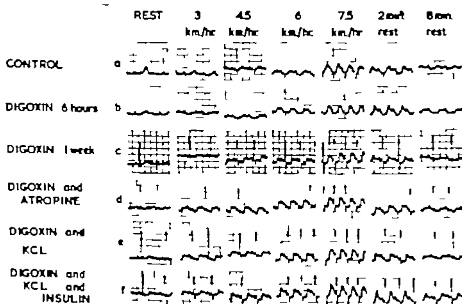


Fig. 2. Electrocardiograms of Subject 9 immediately after light, moderate, and severe effort, and during recovery.

and was, therefore similar to atropine. On the other hand potassium with insulin progressively elevated the T waves at all levels of effort. The S-T segments were much less affected at submaximal work loads. Immediately and at 2 minutes after 7.5 Km./hr., however there was a major albeit temporary decrease in the magnitude of the digoxin induced S-T segment depression. After 8 minutes of rest, the S-T segment was depressed again.

Discussion

Potassium with insulin caused an apparent decline in digoxin-induced S-T segment depression in the exercise electrocardiogram particularly after strenuous work levels. It also caused an increase in the height of T waves after exercise which had been lower previously with digoxin alone. Furthermore the T wave elevation after effort was greater than in the control exercise electrocardiograms and occurred

after light as well as strenuous work levels (Fig 2)

It is difficult to say whether the decline in S-T segment depression produced by potassium with insulin was independent of or a consequence of the elevated T waves. Furthermore in Fig 2,f the apparent partial S-T segment reversion and T wave elevation with potassium and insulin might have been associated with a change in direction of the QRS vector which occurred at increasing levels of exercise On the other hand a similar change also occurred in the exercise electrocardiograms with digoxin alone (Fig 2,c) A comparison of the two exercise electrocardiograms (Fig 2,c and f) after 2 minutes of rest suggests that the T wave elevation and possibly the partial S-T segment reversion in Subject 9 actually occurred as a result of potassium with insulin.

The ability of insulin to alter digoxin induced ST T wave depression suggests that insulin facilitated the entry of potassium into the myocardial cell even in the presence of digoxin It suggests also that a relatively rapid increase in intracellular potassium was instrumental

The above-mentioned results are compatible with the finding that digitalis in nontoxic doses causes a net efflux of potassium from the myocardium[3,4] Anoxia has been thought to account for both digitalis-induced S-T segment changes[5] and T wave elevation after severe effort.[6] The present results suggest that the causes for these two phenomena are indeed metabolic and may be manifold and complex.

It seems clear that the results of this experiment depended on effort, since none of the resting electrocardiograms before the exercise tests showed T wave elevation (Figs. 1 and 2) Effort brings about the mobilization of potassium from working muscles. Increased sympathetic activity likewise tends to increase available potassium[7] It is conceivable that increased myocardial contraction and tachycardia[8] particularly in the digitalized subject causes a decrease in cardiac intracellular potassium which is more readily replaced after the effort has stopped in the presence of insulin It might then be this facilitated repletion of intracellular potassium which accounts for the major increase in T wave amplitude and perhaps, the diminution of S-T segment depression Potassium was given in order to avoid insulin induced hypokalemia. Since hypokalemia itself *causes ST T depression in the exercise* electrocardiogram[2] it could not account for the present observations.

Levels of serum potassium were not determined because they were considered to be a poor indication of rapid myocardial changes. The subjects did not experience any symptoms of hypoglycemia until ½ to 1 hour after testing when slight tachycardia and restlessness occurred in one subject Hypoglycemia[9] causes ST T depression and epinephrine[10] depresses T waves. Likely neither can account for the above mentioned findings.

Summary

Two digitalized subjects who consistently developed progressive ST T changes in their exercise electrocardiograms were treated with oral potassium chloride with and without insulin

Potassium chloride with insulin caused progressive elevation of the T waves and a diminution in the appearance of the S-T segment depression with effort

Possible implications of these findings are discussed

Addendum

Since this paper was submitted for publication Kawai and associates[11] have demonstrated partial reversion of effort induced S-T depression in normal subjects taking digoxin This was brought about by the oral administration of potassium salts.

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Effect of size of cuff bladder on accuracy of measurement of indirect blood pressure

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The standard sphygmomanometer cuff currently used in this country for measuring indirect blood pressure in the upper arms of adults has an inner pneumatic bladder that is 12 cm. wide and 23 cm. long. These specifications for the size of the bladder were recommended by an Anglo-American expert committee in 1939.[1] In 1951, an American Heart Association committee[2] recommended that the bladder have a width 20 per cent greater than the diameter of the arm, and a length sufficient to half encircle the arm, provided that the bladder is placed on the side of the compressible artery. The standard size of 12 by 23 cm. would satisfy this recommendation, except in obese arms which exceed 37 cm. in circumference.

More recently, committees of the World Health Organization[3,4] have suggested using cuffs with bladders 14 cm. wide and long enough to encircle the arm.

The different opinions concerning the size of the cuff bladder expressed by these committees stimulated the following study. It was designed to investigate whether comparability of indirect and direct blood pressure is altered by using cuffs with bladders wider or longer than the standard size of 12 by 23 cm. The study was carried out on subjects having a wide range of arm sizes, so that the relationship of cuff size to arm size could also be examined.

Selection of subjects

Volunteers drawn from among hospital inpatients and medical personnel were considered for the study only if they had a regular cardiac rhythm and nearly equal blood pressures in the two arms. Blood pressures in the upper extremities were judged to be nearly equal if auscultatory readings, made in rapid consecutive fashion in the two arms with a standard cuff, differed by no more than 5 mm. Hg for systolic and diastolic pressures. Volunteers

From the University of Colorado Medical Center, the Denver Veterans Administration Hospital, and the Colorado State Department of Public Health.
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Table I Pertinent descriptive information on subjects arranged according to arm circumference

Subject	Arm circumference (cm.)	Skinfold thickness (mm.)	Age, Race, Sex	Mean indirect blood pressure mm. Hg (16 readings)	Mean direct blood pressure mm. Hg (16 readings)	Clinical comments
1.	21	12	58, W, F	132/77–73	137/73	
2.	22.5	10	31, W, F	100/70–66	110/60	
3.	25	11	53, W, M	100/60–57	106/58	
4.	25.5	7.5	42, W, M	122/76–72	112/64	
5.	27	5	24, W, M	110/60–50	114/67	
6.	27	5	52, W, M	108/73–70	110/65	
7.	27	9	24, W, M	128/92–82	135/86	
8.	27.5	13	53, W, M	135/105–92	140/75	Aortic stenosis
9.	29	7	60, W, M	129/96–90	132/87	
10.	29	7	66, W, M	185/88–82	189/71	Aortic stenosis and insufficiency
11.	30	5	41, N, M	200/139–135	198/132	
12.	30	12	23, W, M	130/74–0	128/74	No organic heart disease
13.	31.5	35	46, W, F	115/82–77	121/80	
14.	32.5	7	31, N, M	132/89–84	140/83	
15.	32.5	5	39, W, M	141/91–88	148/85	
16.	33	15	25, W, M	119/71–63	123/71	
17.	33.5	8	44, N, M	171/100–87	183/83	
18.	34	30	65, W, M	159/93–86	160/75	
19.	34	27	27, W, F	132/75–69	121/70	
20.	35	21	43, W, M	147/ –103	161/97	No muffling of sounds
21.	36.5	12.5	44, N, M	127/97–93	131/90	
22.	36.5	47	46, W, F	139/95–92	139/83	
23.	37	28	26, W, F	135/77–67	132/77	
24.	45.5	44	58, W, M	132/ 96	125/89	No muffling of sounds

who met these requirements were selected primarily on the basis of arm size. Twenty-four subjects, representative of the range of arm sizes and blood pressures seen in the general population, were admitted to the study (Table I). Both the circumference of the upper arm and the thickness of skinfold were measured, the former at a point midway between the acromial and olecranon processes, and the latter over the triceps area by a method previously described[6] using calipers with a spring tension of 10 gm. per square millimeter.

Methods

Both direct and indirect blood pressures were measured with the subject in a supine position. To obtain intra-arterial pressure a percutaneous puncture of the brachial artery was performed with a thin-walled No. 18 needle (right arm in 13 subjects, left arm in 11). After a plastic guideline had been inserted, the needle was removed and a PE 160 polyethylene catheter was advanced 2 or 3 inches inside the artery. Intra-arterial pressure was registered on an oscillographic recorder* via a P23Db Statham strain gauge attached to the catheter and positioned at a midchest zero reference point.

Indirect blood pressure was measured in the opposite arm, using eight cuffs which varied in bladder size and type of fastening (Table II). The cuffs were applied to the upper extremity in strictly randomized sequence, with the lower edge of the cuff placed 4 cm. above the antecubital fold and the inner bladder centered over the flexor surface. Two observers each made a single auscultatory blood pressure meas-

*Electronics for Medicine, White Plains, N. Y.

Table II Bladder size and type of fastening for special cuffs

Bladder size (cm.)	*Fastening*
12 × 23	Hook and rib
12 × 23	Velcro
12 × 35	Hook and rib
12 × 35	Velcro
14 × 23	Hook and rib
14 × 23	Velcro
14 × 35	Hook and rib
14 × 35	Velcro

urement with each cuff The same two observers made all indirect measurements throughout the study using the ordinary clinical method of stethoscope bell placed over brachial artery

To insure unbiased recording of indirect blood pressure a special sphygmomanometer was used (Fig 1) This instrument fully described elsewhere[6] contained a source of compressed carbon-dioxide gas and three mercury manometers hidden from the view of the observer listening to the Korotkoff sounds. After the arm cuff had been attached to the sphygmomanometer pressure within the cuff and manometers was increased by the compressed gas until the radial pulse was obliterated The influx of gas was shut off by the observer and pressure fell at a controlled rate of 2 mm Hg per second When the initial Korotkoff sound was heard the observer pressed a valve which stopped the fall of mercury in manometer 1 thus registering systolic pressure. At the point of sudden muffling of sounds the fall of mercury in manometer 2 was stopped thereby registering diastolic pressure (phase 4) In a similar fashion manometer 3 registered diastolic pressure (phase 5) at the point of complete cessation

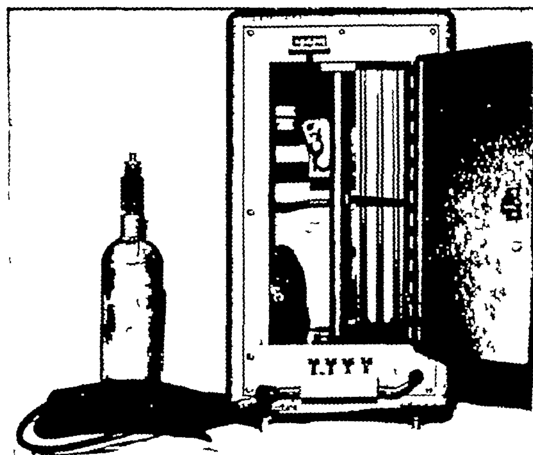


Fig 1 Special sphygmomanometer

of Korotkoff sounds. The pressure in each manometer was recorded by an assistant who was also responsible for changing the cuffs on the arm. In this way neither observer was aware of the results of his own auscultatory measurements or those of his partner.

Measurements of indirect pressure were accompanied by simultaneous recordings of intra-arterial pressure. A base-line signal indicated on the direct record the points at which the auscultatory observer noted the appearance and disappearance of Korotkoff sounds. The average measurement of three systolic peaks (or diastolic troughs) immediately preceding each base-line mark was used for direct pressure.

Although both muffling and disappearance of Korotkoff sounds were recorded, disappearance of sounds was used as the index of indirect diastolic pressure in the analysis of data. One subject (No. 12 in Table I) was excluded from the analyses of diastolic pressure because Korotkoff sounds were audible even with complete deflation of the cuff.

Results

In the analyses of data all indirect measurements of pressure were considered to be deviations from the simultaneous direct readings, e.g., if indirect systolic pressure was 132 mm. Hg and direct pressure was 137 mm. Hg, then indirect systolic pressure was labeled −5 mm. Hg. Thus, in the discussion of results, all references to indirect pressure should be understood as meaning "relative" pressure (deviation from direct reading) rather than absolute pressure.

Observer variation. There was no significant difference between auscultatory measurements made by the two observers. Observer I tended to measure indirect pressure slightly higher than did Observer II, averaging for all subjects 1.2 mm. Hg higher for systolic pressure and 1 mm. Hg higher for diastolic pressure.

Cuff fastening. As shown in Table II there were four pairs of cuffs with varying sizes of bladders. Each pair consisted of a cuff with hook-rib fastening and another with Velcro fastening. Comparison of indirect measurements obtained with each pair having different fastenings but the same size of bladder showed no significant difference.

Width of bladder. Four cuff bladders were 12 cm. wide, and four were 14 cm. wide. Those cuffs with wider bladders yielded lower measurements of indirect blood pressure, averaging for all subjects 3.0 mm. Hg less for both systolic and diastolic pressures than measurements with cuffs having 12-cm. bladders. This represented a statistically significant difference ($p < 0.001$) which was independent of length or fastening. The difference was significant for the entire range of arm circumferences and skinfold thicknesses studied and was not confined to those subjects who were considered to have very large arms (Nos. 21-24 in Table I).

Length of bladder. There were four cuffs with bladders 23 cm. long and four with bladders 35 cm. long. Indirect measurements with cuffs having 35-cm. bladders were lower than those with cuffs having 23-cm. bladders, averaging for all subjects 4.2 mm. Hg less for systolic pressure and 3.8 mm. Hg less for diastolic pressure. These differences were statistically significant ($p < 0.001$) and independent of width and fastening. As with bladder width, the difference was not restricted to those subjects with larger arms but was present in the entire range of arm circumferences and skinfold thicknesses studied.

General size of bladder. Fig. 2 depicts the effect that the size of the cuff bladder had on the indirect measurement of systolic blood pressure. The values for indirect pressure are relative to simultaneous intra-arterial readings. Thus a plus sign indicates indirect pressure greater than corresponding direct pressure. Each circle represents the mean of four measurements (two observations with each of two cuff fastenings) on a single subject. Indirect readings obtained with cuffs having bladders 12 by 23 cm. in size were highest; those obtained with cuffs having bladders 14 by 35 cm. in size were lowest. Readings intermediate to these two extremes were obtained by substituting cuffs with bladders either wider (14 cm.) or longer (35 cm.) than the standard size of 12 by 23 cm.

Fig. 3 illustrates the effect of the size of the cuff bladder on the indirect measure-

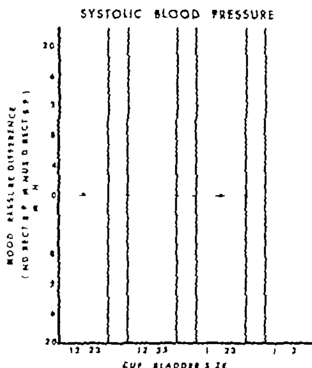


Fig. Indirect-direct systolic blood pressure relationships for 24 subjects with four sizes of cuff bladder. Each circle represents the mean of four measurements for a single subject.

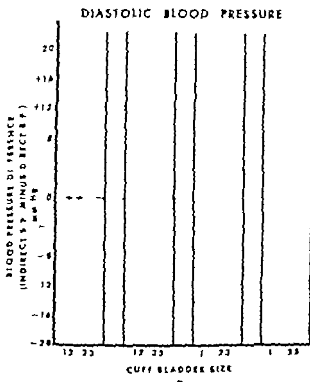


Fig. 2. Indirect-direct diastolic blood pressure relationships for 23 subjects (Subject No. 12 in Table I excluded) with four sizes of cuff bladder. Each circle represents the mean of four measurements for a single subject.

Table III. Difference between direct and indirect blood pressures in all subjects with cuffs having four different sizes of bladders*

	Systolic			Diastolic		
Bladder size (cm.)	Mean pressure difference† (mm. Hg)	Standard deviation	M.S.E.‡	Mean pressure difference† (mm. Hg)	Standard deviation	M.S.E.‡
12 x 23	+1.0	±10.4	110	+5.9	±10.4	115
12 x 35	−3.7	± 5.7	46	+1.7	± 8.1	67
14 x 23	−2.5	± 9.8	103	+2.5	± 9.1	89
14 x 35	−6.3	± 6.9	87	−1.0	± 8.5	72

*One subject (No. 13 in Table I) was excluded from the analysis of diastolic pressure.
†Indirect pressure minus direct pressure.
‡Mean square error = $\frac{\text{Sum of (deviations)}^2}{\text{Number of observations}}$

ment of diastolic blood pressure. Although the scatter of readings with *all* cuffs is greater than for systolic pressure, the trends are the same: highest readings with bladders 12 by 23 cm. in size, lowest readings with bladders 14 by 35 cm. in size, and intermediate readings with the other two sizes of bladder.

Table III shows the mean difference between indirect and direct pressures (systolic and diastolic) in all subjects for the four sizes of bladder. A plus sign indicates indirect pressure *higher than* corresponding direct pressure. Also shown are values for standard deviation and mean square error, both indicative of the amount of intersubject variation. Although the cuffs with bladders 12 by 23 cm. in size showed the smallest mean indirect-direct difference for systolic pressure, they yielded the largest difference for diastolic pressure and showed the greatest amount of intersubject variation. On the other hand, cuffs with bladders 12 by 35 cm. showed the least intersubject variation and yielded indirect measurements that were reasonably close to direct systolic and diastolic pressures.

Discussion

Von Recklinghausen[7] is credited with first recognizing that the width of the sphygmomanometer cuff *can affect* the accuracy of indirect measurement of blood pressure. Finding that the 5-cm. wide cuff designed by Riva Rocci[8] yielded falsely elevated indirect measurements, von Recklinghausen substituted wider models in a search for an accurate instrument. He noted that progressively lower indirect pressure resulted from progressively increasing cuff widths up to 12 cm. Using cuffs beyond a width of 12 cm. had negligible effects on indirect pressure, except in some persons with large arms for whom cuff widths up to 15 cm. were necessary. Other investigators[9, 10] and later authors[11, 12] agreed that a minimum cuff width of 12 cm. was desirable for use on the arms of adults.

Acceptance of 12 cm. as a minimum cuff width did not settle the question concerning the *optimum* cuff width for all sizes of arms. Smirk[13] and Nukada and associates[14] have reported that, contrary to von Recklinghausen's original observations, increasing the cuff width beyond 12 cm. does yield appreciably lower indirect pressure in subjects with arms of *normal size* as well as in those with larger arms. In both studies, made without comparative direct measurement of pressure, indirect readings with 14-cm. cuffs averaged 2 to 4 mm. Hg lower than those with 12-cm. cuffs. Ragan and Bordley,[15] who *did* measure intra-arterial pressure, compared measurements obtained with cuffs having bladders 13 and 20 cm. wide. With the 13-cm. size, favorable correlations of indirect and direct pressures were obtained in subjects

with *arm circumferences up to 34 cm* in 3 subjects with *arm sizes exceeding 34* cm the smaller cuff grossly overestimated the actual direct pressure The 20-cm cuff improved the accuracy of indirect measurement in these 3 obese subjects, but underestimated direct pressure in those with arms of normal size

Other studies using cuffs with bladders 12 or 13 cm wide have compared *indirect-direct pressure relationships in* subjects with *normal and large arms In* general all these studies showed a greater *disparity between indirect and direct pressures* in persons with obese arms. This disparity however can be in the direction of underestimation of direct pressure[17,38] as well as overestimation

These problems in the accurate assess*ment of indirect blood pressure in the* obese arm have led to suggestions for wider cuff bladders. The 1951 American Heart Association committee report[3] recommended that the width of the bladder be 20 per cent greater than the diameter of the arm This means that in arms which reach or exceed a circumference of *37 cm (roughly 12 cm in diameter) a cuff bladder* at least 14 *cm* wide should be used Smirk was even more conservative he suggested that bladders 14 cm wide be used on any arm having a circumference of 29 cm or greater The World Health Organization committee recommended the adoption of the 14-cm size for measure*ment of blood pressure in all adults,* regardless of the size of the arm

Until recently far less attention has been devoted to ascertaining the optimum length for the pneumatic bladder Many reports dealing with indirect measurement of pressure have failed to mention the length of the cuff bladder used in the investigations. Apparently a *feeling has* prevailed that as long as an extremity is completely encircled by some inextensible cuff material the length of the inner pneumatic bladder has much less importance than its width The 1939 joint English and American expert committee report[5] did recommend a *bladder length of 23* cm but cited no *supporting reference* The study reported by Barett and La Place[21] *in* which excellent correlation between direct and indirect pressures was found in *canine thighs using a cuff with a* bladder *12 5 by 22 cm in size may have influenced* the recommendation of the committee.

Nukada and associates,[14] using cuffs with bladders that varied in length between 18 and 30 cm. showed that longer bladders tended to yield lower indirect pressure The difference in readings among the various lengths was significant however *only for systolic pressure in subjects who* had *arm circumferences of 30 cm or more* Intra arterial pressure was not *measured*

Karvonen and associates[22] examined indirect-direct pressure relationships with two cuffs having bladders of different sizes 12 by 23 cm. and 14 by 40 cm. They found that significantly lower indirect pressure and less intersubject variation resulted *from the use of the larger bladder However it was not possible to judge how* much the width or the length alone was contributing to this effect. In addition subjects who had arm circumferences exceeding 32 cm were not represented in the study

The results of our study confirm that either a *widening or a lengthening of the standard* bladder *size of 12 by 23 cm.* produces lower indirect pressure. Of importance is the fact that this effect was as great in subjects with arms of normal circumference as it was in those with large arms Although the substitution of a cuff bladder that differed from the standard *size in width alone (14 by 23 cm vs. 12 by 23 cm) did result in* significantly lower indirect pressure the wider bladder did not appreciably alter the large intersubject variation attributable to the narrower model On the other hand the bladder that differed from the standard size in length alone *(12 by 35 cm vs. 12 by 23 cm) not only* yielded lower indirect pressure but also considerably reduced intersubject variation The largest bladder size (14 by 35 cm) also reduced intersubject variation but showed the poorest correlation with direct systolic pressure

On the basis *of our study we would select the cuffs with bladders 12 by 35 cm in size as* yielding the best results, defining as best the cuffs which showed the least intersubject variation and gave reasonable

correlation with direct pressure. This is not meant as an endorsement of the 35-cm length as optimum for sphygmomanometer cuff bladders. Further study is needed to elucidate the optimum length. However we do believe that serious consideration should be given to use of pneumatic bladders longer than those now available in this country.

Summary and conclusions

Comparisons of indirect and direct blood pressures were made in 24 subjects with sphygmomanometer cuffs varying in bladder size and type of fastening. Results showed that readings obtained with cuffs having book-rib or Velcro fastening did not differ significantly. Significantly lower indirect pressure resulted however with the substitution of cuffs that had bladders either wider (14 cm.) or longer (35 cm.) than the standard size of 12 by 23 cm. Cuffs with bladders 12 by 35 cm were judged to have yielded the best results, since they showed indirect readings that correlated reasonably well with direct pressure and gave the least intersubject variation. It is recommended that strong consideration be given to the use of sphygmomanometer cuff bladders longer than the standard 23-cm length now available for the measurement of blood pressure in adults.

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The fallacy of applying the Poiseuille equation to segmental arterial stenosis

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An adequate quantitative characterization of flow through stenoses in major vessels does not appear to exist. Reported attempts have suffered from paucity of observation and lack of precision, and various reports disagree widely.[1-3] Poiseuille's equation, although often mentioned, is not applicable since it was formulated from experiments in which the laminar flow of water through capillary tubes of even diameter was studied:[4]

"*Il était donc nécessaire d'étudier l'écoulement des liquides dans les tubes dont la capacité approchât de celle des vaisseaux capillaires de l'économie, en cherchant à découvrir les phénomènes qui leur appartiennent exclusivement: tel est le but que nous nous sommes proposé d'atteindre dans les Mémoires que nous avons l'honneur de soumettre au jugement de l'Académie.*"[4]

It is not to be expected (1) that this law would hold for a non-Newtonian fluid like blood, or (2) that it would apply to conditions of turbulent flow, and, furthermore, (3) the radius to the fourth power function refers specifically to the radius of the entire conduit, not just to that of an interposed stenosis.

Failure to appreciate these three facts has led to frequent errors in thinking. Despite its inapplicability, it is still useful to refer to Poiseuille's equation to show how turbulent flow past a stenosis differs from laminar flow, for indeed the same variables are pertinent. This equation, as usually employed or derived by others,[5] is as follows:

$$Q = \frac{\Delta P r^4 \pi}{8 \eta L}$$

where Q = flow, ΔP = differential pressure at the two ends of the tube, r = the radius of the tube, η = viscosity of the fluid, and L = length of the tube.

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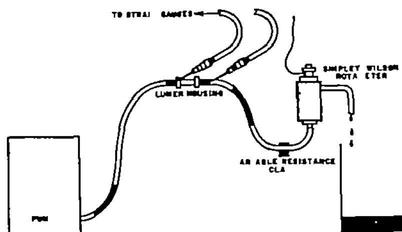


Fig. 1. Assembly for testing flow through various stenotic inserts.

In this paper we shall report on the fundamental relationships of flow through stenoses of precisely measured internal diameter and different lengths, with observations on differential pressure and viscosity. In addition to the empirical observations, a mathematical treatment of the data led to the formulation of an equation for flow through stenoses which may prove to be a convenience to other workers in this field and may serve as a basis for reasoning about the magnitude of effects to be expected by altering variables in a stenotic system.

Methods and materials

The apparatus and stenoses tested. Liquids were pumped through an assembly (Fig. 1) which included a housing for lumens of varying dimension, each constituting a stenosis within the system. Pumping was effected by a constant source of raised air pressure or a pump utilizing intermittent compression of plastic tubing, and latterly by a rotary vane pump. End pressures were measured by needles inserted proximal and distal to the stenoses and connected to strain gauges. Flow was determined by the Shipley Wilson rotameter or when appropriate by collection. Signals from the pressure and flow transducers were fed into a multichannel recorder. The temperatures of pumped fluids were monitored by a bimetallic needle probe inserted proximal to the stenosis housing and connected to a Dermalor thermometer. This enabled us to be aware of changes in viscosity due to heating within the pump.

Differential pressures and flow were varied over a wide range by utilizing various driving or proximal pressures, or by the adjustment of a clamp on the tubing beyond the lumen tested, thus producing a range of distal resistances. A series of lumens 1.5 cm. long was created by drilling holes of measured diameter from 3.12 to 0.67 mm. in blocks of metal and of plastic.

The factor of length of stenosis was studied by serially inserting into the assembly 10 segments of Pyrex glass tubing that varied in length from 1.5 to 15 cm. Four sets of such tubing were employed with bore diameters of 0.75, 1.0, 1.5, and 3.0 mm.

Fluids used and their viscosity. Water, dextran* solution, human plasma, and citrated human blood at room or body temperatures, and propylene glycol were employed. The human blood used in each experiment was all of the same type. Since it was outdated for transfusion, it showed some hemolysis and considerable fragility. Further hemolysis of the blood was observed in the course of the experiment, particularly when it had to be rerun for a series of tests. Hemolysis was least with the steady flow obtained when the blood was pumped by the raised air pressure. It

*Kindly supplied by Pharmachemical Corporation, Bethlehem, Pa.

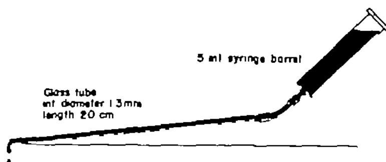


Fig. 2. Hydrostatic viscometer. The time required for 4 ml. of fluid to flow through the device is determined by a stop watch and compared to water.

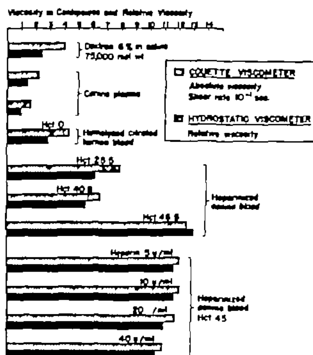


Fig. 3. Relative viscosity using the hydrostatic viscometer for various liquids, compared to readings by Couette viscometer.

was more with external compression pumping and was so great with the rotary vane pump as to prevent the use of this device when the flow of blood was tested. Frequent observations of hematocrit and viscosity had to be made in order to be aware of changes in these factors.

Relative viscosity was determined by a simple hydrostatic device (Fig. 2) by noting the time required for 4 ml. of each liquid to flow through it compared with the time required for the same quantity of water. A comparison of results for various liquids with those obtained with a Couette viscometer showed the simple device to be reliable (Fig. 3).

Results

Dynamics of the short segment (1.5 cm.) stenoses. That flow was turbulent past the stenotic inserts could be observed by the injection of India ink into water pumped both as steady and as pulsatile flow. Turbulence was minimal at the entrance but

more marked distal to the stenosis. It increased with increased pressure and flow and with the severity of the stenosis.

Fig 4 presents the data for human blood passed through four different lumens. The straight line relationship expected in laminar flow is not found instead the linear plot for each lumen shows a deviation attributable to a loss of propulsive energy dissipated in turbulence. Similar curves were found whether the lumens constituted stenoses in a very large-bore or small-bore tubing or whether the flow was steady or pulsatile This aspect of the results is emphasized in a previous publication.[8] Finally the curves were similar for all the fluids used except that for any given lumen and pressure, flow was less as viscosity increased This will be discussed subsequently

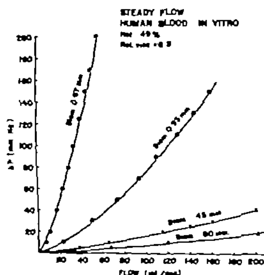


Fig 4 Influence of short stenosis on flow of citrated human blood at varying levels of differential pressure. Steady (nonpulsating) flow driven by raised air pressure over reservoir

In order to describe these curves mathematically they were plotted on log-log paper where they are converted to straight lines as shown in Fig 5 They can therefore be described by the following equation

$$\log \Delta P = b \log F + a$$

or $$\Delta P = F^{b} 10^{a}$$

thus, $$F = \sqrt[b]{\Delta P / 10^{a}}$$

where ΔP is the differential pressure across the stenosis F is the flow through the lumen in milliliters per minute b is the

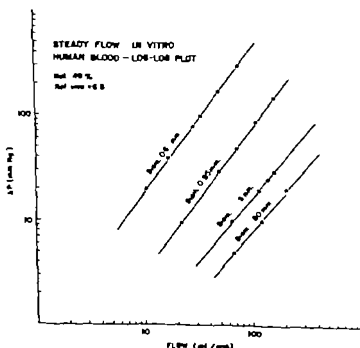


Fig 5 Replot of data from Fig 4 on log-log paper

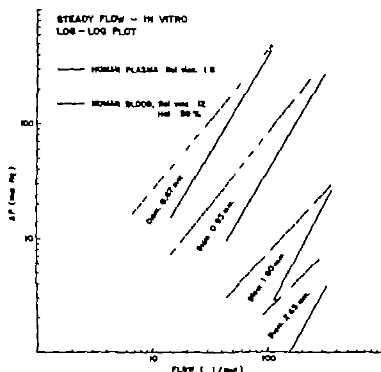


Fig 6 Log-log plot for human blood, as in Fig 5 compared with values for human plasma.

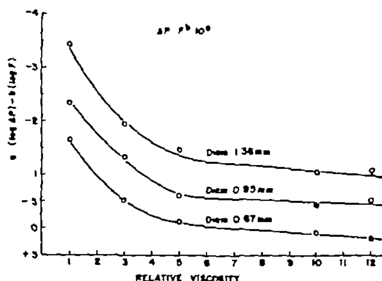


Fig 7 Relationship of exponent *a* to viscosity and radius of stenosis. If viscosity is given *a* varies with the radius of the stenosis.

slope of the curve and *a* is its intercept as calculated from *b* *F* and ΔP

Fig 6 illustrates log log pressure-flow plots for two fluids of different viscosity (plasma and blood with a hematocrit of 59 per cent) flowing through the same four lumens. It is suggested by this graph that the slope *b* of the plots is related to the viscosity of the fluids and the intercept *a* is related to the size of the lumen (degree of stenosis) once the viscosity is specified Figs. 7 and 8 show the behavior of these empirical exponents over the range of variables studied in our experiments.

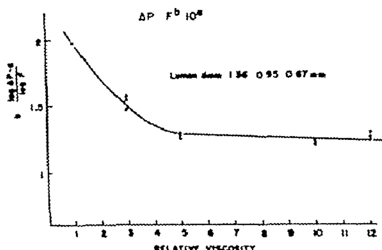


Fig. 8. Relationship of exponent *b* to viscosity. There is close approximation of results for the three different diameters used, emphasizing that exponent *b* varies principally with changes in viscosity.

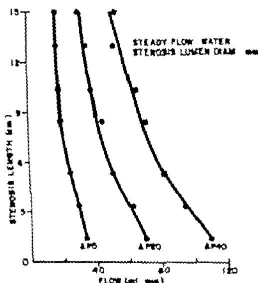


Fig. 9. Influence of length of stenosis on flow for three differential pressures. Flow is only slightly reduced as the length of stenosis is extended.

Stenosis of varying length. Fig. 9 is a plot of the length versus flow for a single diameter of stenosis at three different differential pressures. This example was chosen from a large number of experiments to show the general effect of increasing length on the fall in flow produced by a stenosis.

Effect of viscosity on stenotic flow. Fig. 10 illustrates the role of viscosity in turbulent flow caused by short-segment stenosis (1.5 cm. length). The three curves show the relationship of viscosity to flow at three differential pressures across the same lumen. It is apparent that there is little further reduction of flow with increases in the relative viscosity beyond 7.

Fig. 11 shows the relationship between viscosity and hematocrit of the human citrated blood used in some of our in vitro experiments. It is shown as a convenient reference for this presentation. It is interesting to note that the viscosity is increased at an increasing rate as the hematocrit is raised beyond the normal range.

Discussion

In this series of experiments we have chosen to study the effects on flow of various arbitrary alterations in the pertinent variables. It has not been possible to investigate all of the other factors which may be imagined to be important, such as inlet configuration, irregularities in wall surface, etc., but it is our opinion, based in part on reasoning and in part on preliminary experiments, that these factors are of secondary importance compared to those that we have explored here. Because the conditions of these experiments are so arbitrary and rigidly defined, the objection may be made that the conclusions will not be useful in reasoning about human pathophysiology. We are not suggesting, however, that our equation could ever

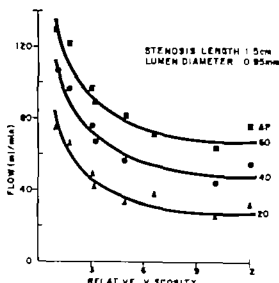


Fig. 10. Influence of viscosity on flow at three levels of differential pressure.

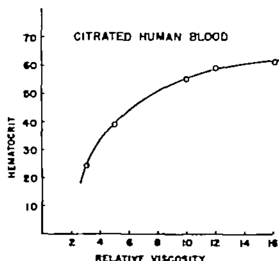


Fig. 11. Relationship between hematocrit of blood and its viscosity. High hematocrit levels are particularly effective in increasing viscosity.

Table I. Radius

Radius (mm.)	Flow Poiseuille (ml./min.)	Flow observed (ml./min.)
0.95	—	120
0.67	29.7	54

Conditions:
Radius = 0.95 mm. → 0.67 mm.
Differential pressure = 50 mm. Hg
Viscosity = 1 relative viscosity unit
Length = 1.5 cm.

Table II. Differential pressure

Differential pressure (mm. Hg)	Flow Poiseuille (ml./min.)	Flow observed (ml./min.)
50	—	54
100	108	78

Conditions:
Differential pressure = 50 mm. Hg → 100 mm. Hg
Radius = 0.67 mm.
Viscosity = 1 relative viscosity unit
Length = 1.5 cm.

Table III. Length

Length (cm.)	Flow Poiseuille (ml./min.)	Flow observed (ml./min.)
3	—	100
15	20	60

Conditions:
Length = 3 cm. → 15 cm.
Differential pressure = 40 mm. Hg
Viscosity = 1 relative viscosity unit
Radius = 1 mm.

actually used to calculate flow in a human artery, but rather that it gives a much closer approximation of the magnitude of the effects of altering diameter and length of stenotic segments, and altering viscosity *and differential pressure (therefore* peripheral resistance as well) than does the misuse of the Poiseuille equation. To that end each variable will be discussed separately below.

We should like to point out in advance *that the effects of all four variables are* considerably less than one would predict from Poiseuille's equation. Tables I-IV contain single examples for clarity's sake but are illustrative of the whole range of data studied. In each table the flow as

Table IV *Viscosity*

Viscosity (*relative units*)	*Flow Poiseuille* (*ml./min.*)	*Flow observed* (*ml./min.*)
1	——	78
11.5	6.8	19

Conditions
Viscosity = 1 R.V.U. → 11.5 R.V.U.
Differential pressure = 100 mm. Hg
Length = 1.5 cm
Radius = 0.67 mm.

calculated by Poiseuille's equation is based on the expected change from the actual flow in the first example when the appropriate variable is altered. That there is a logical fallacy in this calculation (i.e. the Poiseuille equation could not have given the correct first value on which the calculation is based) further illustrates the absurdity of applying the equation to this problem.

Radius. We have previously reported, as have others, that an increasing stenosis does not have any appreciable effect until the resistance across it is a significant part of the total resistance across the system. Thus halving the diameter of a tube in a short stenotic segment does not reduce the flow to one sixteenth of the original value, as would be predicted from Poiseuille's equation, but, in fact, has no measurable effect. Table I shows that even in a range in which decreasing the diameter of the stenosis has a profound effect on the flow, it is, nevertheless, considerably less grave than the use of Poiseuille's equation would lead one to predict.

Differential pressure. In the previous paper mentioned[1] we pointed out that the differential pressure across a stenosis and the flow through it show a fairly close inverse proportion with increasing stenosis, and that the flow through a stenosed vessel is the same fraction of the unobstructed flow (with the peripheral resistance unchanged) as the distal pressure is of the proximal pressure. However, it is clear from Table II that there is not a direct linear relationship between differential pressure and flow in a turbulent system. In general, the expenditure of a given amount of pressure energy results in less flow than in a nonturbulent system, the balance of pressure energy being dissipated in the production of turbulence. Referring to Table II, we see that doubling the differential pressure does not double the flow, as one would predict from Poiseuille's equation, but only increases it by about one half in this example.

Length. The factor of length is of much less significance than the diameter of a stenosis with respect to hindering flow through that stenosis. It is for this reason that we felt justified in performing all of our experiments, except those in which length was the variable, with a standard stenosis length of 1.5 cm. One can look upon a stenosis as having two separate resistance effects—one consisting of the wall friction (drag) of the tube, the other of the dissipation of energy in turbulence. Only the first would be expected to increase as the stenotic segment is lengthened, and this is usually the lesser of the two effects. Thus, Table III shows that a fivefold increase in the length of a 1 mm. diameter stenosis reduced the flow to only 60 per cent of its former value, rather than to the 20 per cent predicted from Poiseuille's formula.

Viscosity. The effect of increasing the viscosity of the fluid is to decrease flow, but this effect is of little magnitude when viscosity is increased beyond about 7 R.V.U. This can be understood if one considers that an increase in viscosity has two separate and opposite effects in a system such as is here considered: the first is to retard flow by increasing drag and the second is to reduce turbulence. Table IV shows that, although an increase in viscosity from 1 to 11.5 R.V.U. (relative viscosity units) profoundly diminishes flow, the effect is much less than would be predicted from Poiseuille's equation.

Summary

1. In order to study the dynamics of flow through stenoses, we have performed a series of experiments in an arbitrary model in which blood and other fluids were passed through stenoses of previously known dimensions in a tubular system

and pressures, flow and viscosity were recorded

2. Our data are summarized by the equation

$$F = \sqrt[b]{\Delta P\ 10^a}$$

where F = flow, ΔP = the differential pressure and a and b are exponents related to the radius of the stenosis and fluid viscosity respectively.

3. Our results reveal the following departures from the Poiseuille equation for flow through stenoses. (a) Flow is not proportional to the fourth power of the radius of the stenotic lumen but varies with its absolute radius in relation to the differential pressure (and therefore is also dependent on peripheral resistance). (b) Flow is not linearly related to differential pressure because energy is progressively dissipated in turbulence as differential pressure rises. (c) Flow is not linearly related to *viscosity* for although an increased viscosity increases drag it also tends to diminish turbulence.

We conclude that the Poiseuille equation does not apply to flow through stenoses.

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Case reports

Becker type cardiomyopathy in a West Indian woman

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The nature and causation of some diseases in which there is involvement of the myocardium and the endocardium is obscure. From a comparison of the lesions in Löffler's disease, endomyocardial fibrosis and one common form of South African cardiomyopathy (Becker's disease) it was concluded[1,2] that these were different entities unrelated to each other. Further studies[3,4] have supported this conclusion in respect to Löffler's disease and to the newly described form of parietal endocardial thickening in which there is conspicuous infiltration of the endocardium with neutrophil polymorphonuclear cells.[5] However Thomson[6] and the Nigerian workers[7,8] have maintained that Becker's disease and endomyocardial fibrosis are sequentially related, the lesions described by Becker representing the early stages of endomyocardial fibrosis, a conclusion which Becker[4] cautiously supports although he details some differences between the two conditions. The difficulties are increased by lack of certain knowledge and agreement on the very early lesions of endomyocardial fibrosis.

We have recently studied a case which seems in essentials to conform closely to the descriptions of Becker's disease and which presents vascular lesions of a type so far not encountered in a large series of cases of endomyocardial fibrosis.

Case history

The patient (No. 262403) was a 22 year-old Negro girl from Dominica, who had resided in London for 13 months, and who had been well until 5 weeks before her death. Her initial symptoms of malaise, cough, dyspnea, hemoptysis, and central chest pain led to her hospitalization on the sixth day. She had also noted diarrhea and abdominal pain for 1 week.

On admission she was obviously ill and dyspneic, with a tachycardia of 130 but no fever. There was herpes of the upper lip. Congestive cardiac failure was present, as evidenced by a high jugular venous pressure, enlarged liver and slight edema. The apex beat was palpable outside the nipple line and there was a soft mitral systolic murmur and a summation gallop. The arterial pulse was of small volume, and there was no pulsus paradoxus. The blood pressure was 110/80 mm. Hg. The rhythm was regular. The venous pulse was of diagnostic importance for it showed a and v waves of equal height (in contrast to the venous pulse of tricuspid incompetence) and indicated that cardiac constriction, either endocardial or myocardial, was present—tamponade being excluded by a negative pericardial tap. There were signs also of a large right pleural effusion.

On the day after admission the left leg became cold and blue and the left femoral pulse was weak. In the following days the foot became gangrenous, and this was assumed to be due to an arterial embolus. Sinus rhythm was still present.

Investigations at this stage showed a hemoglobin of 13.3 Gm. per cent, a leukocyte count of 19,900 (polymorphs 80 per cent), and no red cell sickling. The urine was normal. Pleural aspiration revealed a yellow fluid with 73 per cent polymorphs which was sterile on culture and from which *Mycobacterium tuberculosis* could not be grown. The electrocardiogram (Fig. 1) showed slight left atrial hypertrophy and considerable left ventricular hypertrophy with T wave inversion over the left

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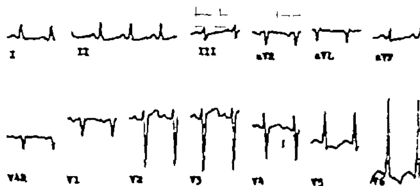


Fig. 1. Electrocardiogram showing broad P wave in Lead V and tall R with inverted T in Lead V₆.



Fig. 2. Chest radiograph showing enlarged heart and right pleural effusion.

ventricle. On examination (Fig. 2) the cardiac silhouette was large and a right pleural effusion was noted.

Her clinical course was one of slow deterioration in spite of the administration of digitalis, diuretics, and antibiotics. The right pleural effusion was aspirated on several occasions. Later a large pericardial effusion developed. Severe normochromic anemia probably due to toxemia from the gangrenous leg necessitated several blood transfusions. The serum albumin fell to 2 Gm. per cent, but the edema remained slight although ascites did develop. She was transferred to Hammersmith Hospital, where amputation of the leg was performed but cardiac arrest developed while she was on the operating table and she died a few hours later.

Autopsy findings. A coroner's postmortem was carried out, and the heart and portions of other organs were made available to us.

The body was edematous, with a large pericardial effusion and a liter of free fluid in the abdominal cavity. There was severe edema of the retroperitoneal tissues. The air passages were full of blood-stained, frothy mucopurulent fluid and the lungs showed severe generalized edema with old and recent infarcts in the tips of the lower lobes; many peripheral vessels showed recent emboli. The liver showed severe nutmeg changes and was very firm, as was the pancreas. The kidneys and other abdominal organs were congested as were the brain and the cerebral vessels.

The heart weighed 462 grams after formol fixation. It was grossly dilated and globular in shape. The right atrium was neither dilated nor hypertrophied; the right ventricle was dilated and hypertrophied (5 mm.) but no thrombus was present. The left atrium was dilated and hypertrophied and the endocardium was thickened and opaque; the appendage contained a fragment of thrombus. The left ventricle was dilated and the wall was 10 to 13 mm. thick. All valves were macroscopically normal (tricuspid 12.5 cm., mitral 12.0 cm.), as were the coronary arteries.

The striking features of the heart were the color and the consistency. The myocardium was a light yellow gray, almost waxy in appearance which (Fig. 3) contrasted sharply with the usual brown-red color of the normal heart. This yellow color was not affected by fixation and was not uniform, for there were areas of normal coloration and the yellow was most intense in the inner portions of the myocardium. The consistency was most peculiar; it was not friable at all but felt and behaved like rubber in that it could be bent and severely distorted without breaking. The third feature was a dull filmy general opacity of the endocardial surface (Fig. 4). The endocardium was not overtly thickened but the opacity was evident in all areas of the left ventricle including the whole septal wall.

Microscopically lesions other than those of congestion were confined to the heart and lungs.

The pericardium showed a minimal degree of pericarditis with occasional minute foci of lymphocytes. The epicardial fat was edematous but there was minimal cellular infiltration. The major coronary vessels were in all respects normal. The myocardium in the outer layers of the heart showed



Fig. 3. Four blocks of heart muscle showing changes in color. The one block of different color to right is normal heart for comparison after formol fixation for the same period.

slight changes of hypertrophy but toward the cardiac cavities the changes became more marked (Fig. 5); the nuclei were hyperchromatic with square, blunt ends and an occasional bizarre shape. There was no vacuolation of nuclei and no vacuolation or pigmentation of the myofiber cytoplasm. The absence of such moth-eaten fibers was striking.

In the inner third of the myocardium changes were apparent in the small vessels; the lesions were patchily distributed but they were also more prominent at the endocardial surface. Near the endocardium were many dilated vascular channels whose walls showed no lesions.

The endocardium was variably thickened, and three components contributing to this thickening could be distinguished. Firstly, there was swelling due to the deposition of basophilic mucoid material; secondly, there was a variable degree of hypertrophy of smooth muscle fibers (Fig. 6); and, thirdly, there was a mild degree of fibroelastotic thickening (Fig. 7) within some endocardial pockets, a mild degree of endocardial fibrosis. Nowhere on the endocardial surfaces were there fibrin deposits, and no fibrin was incorporated into the thickened endocardium. There was no marked cellular infiltration but some collections of cells were found in the endocardium adjacent to the areas of mucinous change (Fig. 8), and in occasional sections white cells were found to be lined up in row along the endocardial surface (Fig. 9).

The smooth muscle hypertrophy was equally patchy. It sometimes showed up as a small eosinophilic region in a basophilic mucoid area and sometimes as a small band. Both the mucinous changes and the smooth muscle changes were more widespread and evident than the fibroelastosis which was very patchy and focal and was seen particularly in the crypts of the trabecular muscle but it was equally evident on the septal wall.

The changes in the subendocardial blood vessels



Fig. 4. Endocardial surfaces showing, on right, endocardial thickening and, on left, subendocardial damage.



Fig. 5. Thickened endocardium with prominent smooth muscle bands and dilated subendocardial vessels with fibrin polyps. The myocardial changes are also shown. Hematoxylin and eosin. ×100.



Fig. 6. Hypertrophy of smooth muscle fibers in an edematous area of the endocardium. Hematoxylin and eosin; ×370.



Fig. 7 Elastotic patchy thickening of the endocardium. L.E.H.V.G. ×100.



Fig. 9 Endocardium. Thickened fibrosed area. Hematoxylin and eosin ×370



Fig. 8 Mucinous edematous patch on endocardium. Hematoxylin and eosin ×370

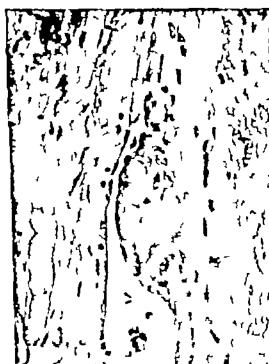


Fig. 10 Small fibrin deposit on wall of small endocardial blood vessel. Hematoxylin and eosin ×370.



Fig. 11 Eccentric fibrous thickening in lumen of small subendocardial blood vessel. Hematoxylin and eosin ×100



Fig. 12 Eccentric cushion in small blood vessel full of capillaries. L.E.H.V.G. ×100.



Fig. 13 Small hyalinized polypoidal cushion in small blood vessel. Hematoxylin and eosin ×100.



Fig. 14 Complete occlusion of small subendocardial blood vessel. Hematoxylin and eosin ×38.

were also focal, and the degree of damage varied greatly. The earliest lesion was the deposition of fibrin in small patches on the endothelium (Fig. 10), forming little warty masses that sometimes were polypoid in shape. There was little cellular infiltration. These masses appeared to undergo progressive transformation into a mass of fibrofibrinous tissue forming an eccentric cushion-like mass that narrowed the lumen, sometimes to the point of complete occlusion (Figs. 11-14). The bases of these masses showed organization, with very marked capillary proliferation, and some vessels were filled with a mass of capillary tissue. No evidence of ischemic lesions in the myocardium was found, and there was no fibrosis either around these altered vessels or around the ectatic vessels with normal endothelium. A very few areas of necrosis of myofibers and of cellular infiltration were found in the myocardium together with a few areas of myocardial fibrosis. Such areas were small, scanty, difficult to find, and haphazardly located, some being in the outer third of the myocardium.

The lungs showed evidence of severe edema, both watery and fibrinous, with evidence of bronchial infection and infarction. But in addition there were areas of platelet thrombus in the alveolar capillaries, with apparent breakdown of capillary walls. There was evidence of a vasculitis with fibrinous exudation affecting both the intima and adventitia of the pulmonary veins, with marked mucoid changes in the intima (Fig. 15). The liver showed an extreme degree of congestion.



Fig. 15. Lung vein with intimal thickening and mucinous change. Hematoxylin and eosin. ×38.

Discussion

The presence of the characteristic venous pulse permitted this patient to be categorized clinically as having constrictive cardiomyopathy,[9] and the autopsy finding of a stiff and rubbery myocardium indicates already the pathologic basis for this state of cardiac constriction. Lesions were found in the inner third of the myocardium and in the endocardium and in the pulmonary vessels. The diffuse opacity of the endocardium was present in all chambers but was most marked in the left ventricle, where apex and both inflow and outflow tracts were affected. The endocardial opacities were due to a combination of mucinous edema and elastomyofibrosis with scanty cellular infiltration and the endocardial and subendocardial blood vessels showed fibrin deposition and fibrofibrinous internal thickenings which varied from polypoid masses to eccentric thickenings to total vessel occlusion with capillary tissue organization. These lesions are precisely similar to those which Becker[4] has described from South Africa in his cases of endomyocardial disease with mural thrombi and Becker[10] has examined sections from this case and remarked that the case "is typical of our South African cardiomyopathies."

The age of the lesions in this patient is difficult to assess; the lack of previous history and the rapid deterioration with embolization would suggest an acute process although the lesions would suggest a more subacute process. It is clear that the typical lesions of Becker's disease have been found in London in a West Indian. Stuart and Hayes[11] have described a common cardiomyopathy occurring in Jamaica in patients whose presentation and clinical progress are similar to those described from South Africa. These Jamaicans have hypertrophied hearts with mural thrombi and endocardial scarring and embolic accidents are frequent. However Stuart and Hayes do not appear to have seen the very typical lesions described by Becker[4] and so clearly evident in our case. Becker has warned however of the focal nature of these lesions and the necessity for multiple sections from many areas to establish their presence and our experience confirms this. We do not know whether this case is really

representative of West Indian cardiomyopathies.

The question which remains is the identity or nonidentity of the mural endomyocardiomyopathies. Is Becker's disease an early and acute stage of endomyocardial fibrosis or are these quite separate and distinct diseases? The particular features of endomyocardial fibrosis is the grossness and severity of the fibrosis, the marked damage to the atrioventricular valves, the limitation to the apex and inflow tract, and the sparing of the outflow tracts, which if involved at all shows merely the endocardial changes due to eddy and turbulence.[2] The endocardial fibrosis is a scar indicating complete destruction of the previous endocardium. In Becker's disease the typical lesions are present in the outflow tract quite as severely as in the inflow tract, as our case shows, and although damaged there was no evidence of destruction of the endocardium. The changes of Becker's disease in the subendocardial blood vessels are not seen in cases of endomyocardial fibrosis in Uganda, where in the early stages there is ectasia and in the late stages a fibrosing obliterative arteritis. After familiarization with the lesions of Becker's disease[10] a search was made for cases in Uganda with such vascular lesions, without success, although they were immediately recognized in this case. The evidence would seem against Becker's disease being an early stage of endomyocardial fibrosis. The etiology of both these conditions remains quite obscure but the need for further detailed reports on the histopathologic changes in tropical cardiomyopathies is obvious.

Summary

A case of cardiomyopathy in a West Indian Negro woman is reported in which the lesions correspond closely to those described in one form of South African cardiomyopathy, Becker's disease. The lesions are described and it appears that they are specific to this disease and dissimilar to those seen in endomyocardial fibrosis.

We are grateful to H. M. Coroner, West London, and to Professor C. V. Harrison for access to material, and to Prof. B. J. P. Becker for his comments. Dr. W. C. Marshall gave valuable help in the management of the patient. The photographs are by Mr. William Brackenbury.

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Ruptured papillary muscle after acute myocardial infarction

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Although first described by Mérat[1] in 1803, only 81 cases of ruptured papillary muscle have been reported.[1-8] This rare clinical entity is usually the result of acute myocardial infarction. The diagnosis was made at autopsy in most of the reported cases; only 12 cases were diagnosed before death. Two additional cases of ruptured papillary muscle after acute myocardial infarction are now reported. In one patient the diagnosis of ruptured papillary muscle was made on the day on which the rupture occurred, 5 days before death; in the other patient the diagnosis was made at autopsy.

Case reports

Case 1. E. P., a 77-year-old man, was admitted to the continuous electrocardiographic monitoring service[9] with a 12-hour history of severe, crushing retrosternal chest pain. He was confused and there was marked pallor; the blood pressure was 150/80 mm. Hg and the jugular venous pressure was elevated 3 cm. On auscultation there was a split first heart sound, but no murmurs. These findings were confirmed by phonocardiogram (see Fig. 1). Examination of the chest revealed bilateral râles and crepitations. An electrocardiogram (see Fig. 2) showed a nodal tachycardia at a rate of 150 per minute, the changes of posterior myocardial infarction, and marked S-T segment depression in the anterior chest leads.

Because carotid sinus massage had no effect on the tachycardia, he was given 0.75 mg. of digoxin intramuscularly and 0.25 mg. of digoxin orally every 8 hours. Chlorothiazide 500 mg. twice daily was begun, but anticoagulant therapy was not employed. Serum glutamic-oxaloacetic transaminase was estimated every 12 hours, and blood urea and urinary output were measured daily (see Fig. 3). The day after admission the erythrocyte sedimentation rate was 42 mm. in 1 hour, hemoglobin 15.8 Gm. per 100 ml., white cells 10,000 per cubic millimeter, serum cholesterol 250 mg. per 100 ml., and total serum lipids 720 mg. per 100 ml.

Over the next 4 days his clinical condition improved, the tachycardia was controlled, and the signs of cardiac failure cleared. However, in spite of a good urinary volume with a fixed specific gravity of 1.010, the blood urea continued to rise (see Fig. 3). Daily electrocardiograms showed persistence of the S-T segment depression in the anterior chest leads. It was considered that these changes were due to associated subendocardial infarction (see Fig. 4).

A moderately loud, Grade 2 (4), pansystolic murmur, maximal at the left sternal edge and well conducted to the left axilla and infrascapular region, was detected on the fifth day after admission (see phonocardiogram, Fig. 1). A systolic thrill was not palpable. The diagnosis of ruptured papillary muscle was made. After this complication there was no significant change in the blood pressure, or heart rate, and pulmonary edema did not appear. However, his clinical condition deteriorated, associated

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Fig. 1. Case 1. The phonocardiogram recorded on May 15, 1964, at the time of the patient's admission to hospital shows a split first heart sound. The second recording obtained on May 20 shows a pansystolic murmur. The recordings were made at the left sternal edge in the fifth intercostal space. Paper speed = 100 mm. per second.

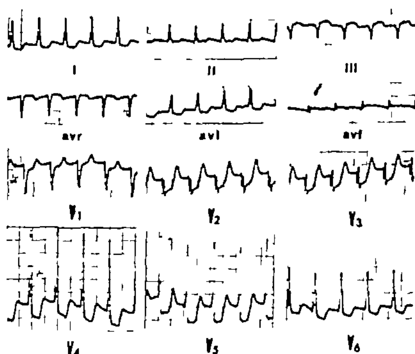


Fig. 2. Case 1. Electrocardiogram recorded on admission, May 15, 1964.

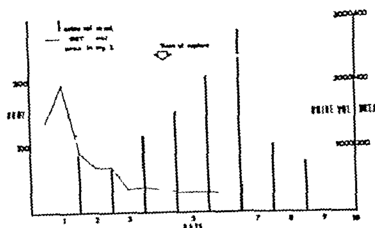


Fig. 3. Case 1. There was a progressive rise in blood urea, and a fall in SGOT from a peak measured level of 197 units.

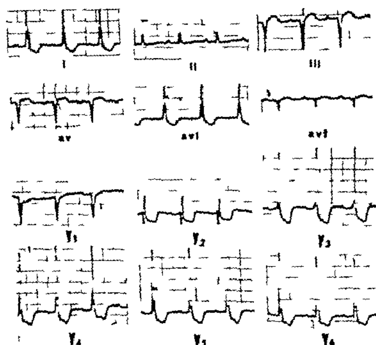


Fig. 4. Case 1. Electrocardiogram recorded on May 20, 1964.

with a progressive rise in blood urea to 615 mg. per 100 ml. and the development of bronchopneumonia. Death occurred 10 days after his admission to hospital.

AUTOPSY. The heart was slightly enlarged, weighing 400 grams. Two centimeters from its origin the right coronary artery was completely obstructed by antemortem thrombus. The circumflex branch of the left coronary artery was obliterated at its origin by calcified atheroma and organized thrombus. There were calcified plaques of atheroma in the wall of the anterior descending branch of the left coronary artery but its lumen was patent.

Transmural infarction involved the posterior superior aspect of the left ventricle and spread inferiorly, becoming mainly subendocardial to involve the entire left posterior papillary muscle. Complete rupture of the left posterior papillary muscle had occurred, 1 mm. above its base (see Fig. 5). Apart from excess mobility of the aortic cusp of the mitral



Fig 5 Case 1 The arrow indic tes the base of the ruptured left posterior papillary muscle

he all cardiac alves were normal, nd the inter entricular sept m was intact

Both kid ey were contracted nd showed scarred irregul r surf es the renal orifices were 3 mm wide Microscopically both kid ey showed the ch nges of nephrosclerosis

Case 2 1 B a 61 year-old man presented to his



Fig 6 Case 2 The arrow indicates the basal segment of the ruptured papillary muscle. The separated portion has passed through a space between the chordae tendineae twisting the chordae.

medi al practitioner with a 2-week history f pain between the scapula nd hortness of bre th A y tolic murmur wa udible and there were râles at both lung bases The patient initially refused admiss n to hospital, but later that day onsented because of increasing hortness of breath

On his rrival t the a lty department, acute pulmonary edema w present, and he wa acutely dyspneic and unable to give a medical history There wa gross central cyanos the radial pulse was impalpable and the jugular enous pressure was elevated 8 cm. There were loud course râles through-o t the hest and the heart sound were inaud ble Before tandard electrocardiogram could be recorded cardiac arrest occurred and attempted resuscitation fa led

AUTOPSY The heart was enlarged, weighing 430 grams. All branches of the left coronary artery were patent whereas the posterior interventricular branch of the right coronary artery was occluded by thrombus

Infarction of the posterior wall of the left en tricle extended from the endocardial surface to just beneath the epicardial surface; the inf rcted zone wa yellow and softened. The proces spread inferiorly invol ing the left posterior papillary muscle which had ruptured completely 1.5 cm. above ts base The separated portion which measured 1 2 cm. had passed through a space between its t tached chordae tendineae thus twisting the chordae (see Fig 6).

Discussion

When a systolic murmur suddenly de velops after acute myocardial infarction the differential diagnosis will include ruptured papillary muscle perforation of the interventricular septum infarction of a

papillary muscle without rupture and left ventricular failure with functional mitral incompetence.

With rupture of a papillary muscle, the pansystolic murmur of mitral incompetence would be expected. In about 60 per cent of the reported cases of ruptured papillary muscle a systolic murmur was detected.[4] In some cases the murmur may not be heard because of the sudden death of the patient after the rupture or, as in Case 2, the heart sounds and murmur may be obscured by the loud râles of acute pulmonary edema. In only 2 of the reported cases was a systolic thrill palpable.[2,3] The left posterior papillary muscle is the muscle most commonly involved and thus is usually associated with the electrocardiographic changes of posterior myocardial infarction.[4]

Perforation of the interventricular septum is accompanied in 95 per cent of the cases by the development of a pansystolic murmur maximal at the left sternal edge in the fourth or fifth intercostal space and a systolic thrill is palpable in over 50 per cent of the cases.[4] In 75 per cent of the cases of ruptured septum the electrocardiogram shows the changes of anterior myocardial infarction.[4] Rupture of the interventricular septum is usually followed rapidly by severe congestive cardiac failure with hepatic engorgement. During the last 18 months, we have observed 3 patients with myocardial infarction and rupture of the interventricular septum. In each case, after rupture there was a rapid and progressive rise in serum glutamic-oxalacetic transaminase to levels above 100 units. Presumably this was derived from both myocardial and hepatic damage.

Infarction of a papillary muscle without rupture can lead to a systolic murmur.[11] In this condition it is postulated that the damaged papillary muscle fails to contract during the ejection phase of ventricular systole, and then the attached segments of the mitral valve cusps will evert into the left atrium. The murmur produced is not pansystolic, but is of a crescendo-decrescendo quality and begins after the first heart sound. Acute pulmonary edema does not commonly follow this complication of myocardial infarction.[11]

Functional mitral incompetence secondary to left ventricular failure will cause a pansystolic murmur. This murmur develops gradually and it will increase progressively in intensity. Burch and associates[11] suggest that in some cases of left ventricular failure the genesis of this pansystolic murmur may be dependent on papillary muscle dysfunction rather than dilatation of the atrioventricular ring.

In Case 1 the association of acute posterior myocardial infarction and subendocardial infarction with a sudden onset of the pansystolic murmur of mitral incompetence, and the absence of a systolic thrill led to the diagnosis of ruptured papillary muscle. The serum glutamic oxalacetic transaminase did not rise after the development of this murmur, which was unlike our previous experience with ruptured interventricular septum.

When rupture of a papillary muscle follows myocardial infarction there is usually a sudden onset of pulmonary edema, and death ensues.[3] The typical clinical course of ruptured papillary muscle is illustrated by Case 2. In Case 1 sudden deterioration of the circulatory state did not occur; instead death was due to renal failure. Breneman and Drake[4] have reported 2 patients with myocardial infarction who survived for 10 and 14 months after rupture of the left posterior papillary muscle. Cooley and associates[12] have discussed the possibility of reparative surgery for ruptured papillary muscle after acute myocardial infarction. They suggest that surgery should be delayed until at least 6 weeks after the acute episode.

Summary

Two cases of rupture of the left posterior papillary muscle after acute myocardial infarction are reported. The diagnostic features of this uncommon complication of myocardial infarction are discussed.

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Clinical pathologic conference

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Clinical abstract

DR. HEATH The patient was a 36-year-old man who was employed as a boxer. His health had been excellent until May 1964 One day during that month he was playing golf immediately after having played a stroke during the course of the game, he suddenly became faint and dizzy He stated "It was just as though my head was spinning." At the same time he developed a "terrific ache" behind the right eye. His legs felt weak and he was unable to walk for more than 30 yards. On this occasion he had no pain in the legs. His legs remained very weak and his eyesight appeared to be deteriorating His general practitioner sent him to an outpatient department for examination and various investigations were carried out.

On June 24 he was seen at the outpatient department again. H still complained of weakness of the legs, headache and dizziness. There were no abnormal signs in the central nervous system. On September 9 he was still having attacks of dizziness and weakness of both legs. His systemic blood pressure was 130/80 mm. Hg There were no abnormal physical signs referable to the central nervous system.

At 8.30 A.M. on September 30, while he was going to work, he was suddenly seized with violent cramplike pains in both calves. The pain was so severe that he could not stand, let alone walk. He w admitted to hospital an emergency case. He stated on admission that he had been a pipe smoker for 12 years, and that he was a light drinker On examination he was obviously in great pain He was not short of breath, and had no pain in the chest. There was no swelling of the ankles The left calf was exceedingly tender but was not swollen There was slight tenderness of the right calf The left foot was cold. There was diminished sensation in the left toes which were cold and bluish in color and which could be moved only with difficulty The right foot was cool. When the patient was first seen, the right and left femoral and popliteal pulses were palpable but no pulses distal to these sites could be felt in either leg Later the left posterior tibial pulse was easily felt. The left calf remained very tender

The systemic blood pressure was 130/90 mm. Hg The radial pulse rate was 92 per minute. The heart was not enlarged and there were no disorders of rhythm. No murmurs were heard. Examination of the abdomen and of the central nervous system revealed no abnormal physical signs.

Investigations The white cell count and differential on October 1 was 9,500 per cubic millimeter neutrophils 70 per cent eosinophils 1 per cent, lymphocytes 24 per cent, monocytes 5 per cent. On October 8 there were white cell count 6,000 per cubic millimeter neutrophils 76 per cent, eosinophils 1 per cent, lymphocytes 20 per cent, monocytes 3 per cent. Lupus erythematosus cells were not seen Serum B level 275 $\mu\mu$Gm per cubic centimeter Serum cholesterol 134 mg per cent. Stools No ova, cysts Salmonella, Shigella, or Staphylococci. Bilirubin 0.5 mg per cent. Thymol turbidity 1 Thymol flocculation, 0 Alkaline phosphatase 11.1 (King-Armstrong units) Serum creatinine level 18 mg per cent Protein-bound iodine 5.3 μGm per cent (normal 3.5 to 7.5 μGm per cent).

Hospital course Therapy was started and his clinical course was as follows. October 2 Developed diarrhea with fresh blood in the stools. Vomited two or three times day Urinary output satisfactory October 5 More blood passed. Barium meal and follow through carried out. October 6 Bled from the lips. Developed hematuria. October 8 Became anuric October 9 Anuria continued A biopsy of the left gastrocnemius muscle was performed. At 5 P.M., retrograde pyelograph was performed. He felt faint and collapsed after this H developed a left hemiplegia. October 12 Semiconscious. Started on peritoneal dialysis October 13 Died.

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Discussion

PROF. GOODWIN: This man felt well until he played this stroke during a game of golf, which of course involved a certain amount of rotation of the spine and physical exertion. He then suddenly felt faint and dizzy; such symptoms do not necessarily imply a disorder of either the cardiovascular or central nervous system, and he may have had, for example, a gastrointestinal hemorrhage. Nevertheless, this patient's description of his head swimming suggests to me a labyrinthine or cerebellar disturbance. The sudden dramatic pain behind the right eye is reminiscent of an acute vascular emergency such as might occur with an embolus. A subarachnoid hemorrhage is another possibility but less likely because of the absence of stiffness of the neck. The whole picture suggests a basilar artery insufficiency syndrome which may produce disturbances of position, vertigo, and oculomotor palsies. The subsequent story of deteriorating eyesight and weakness of the legs that made him incapable of walking more than 30 yards is consistent with some arterial disease such as giant cell arteritis affecting both cranial arteries and branches of the lower aorta. I favor an arteritis rather than multiple systemic emboli because at the moment I can find no clue to a source for such emboli.

The common causes for systemic embolism include the following: *Atrial fibrillation with mitral valve disease*, for either of which there is no evidence from the clinical history. A burst of fibrillation may occur and then revert to sinus rhythm, but even so I should have expected the signs of mitral disease. *Subacute bacterial endocarditis* is another important cause of systemic embolism, but there is no suggestion of it in this case. Then a *myocardial infarct* or *cardiomyopathy* may be associated with mural thrombus which may give rise to emboli. Fourthly, embolism in the systemic circulation may arise from a *left atrial myxoma*, but here we are becoming more esoteric. Finally, *atherosclerosis* may provoke thrombus formation and embolism. However, the lack of an obvious source for emboli leads me to believe that we are dealing with an arteritis producing basilar artery insufficiency.

The progressive deterioration in vision is difficult to explain. It could have been due to involvement of the retinal artery, but it could also have been brought about by optic neuritis or papilledema, such as might be associated with malignant hypertension or a cerebral tumor. However, it is more likely to be due to some lesion in the retinal artery, for there is no mention of headache, abnormal signs in the central nervous system, or hypertension. I note that the radiograms of the skull and cervical spine were normal.

The dramatic events of September 30 also suggest to me some acute vascular emergency involving the bifurcation of the aorta and the arteries of the lower limbs. This could be due to a dissecting aneurysm, but the pain in the eye and the dizziness do not seem to fit in with that diagnosis. Once again the story is more like that of emboli, possibly breaking up from a saddle embolus. What is the source of these emboli: atherosclerosis or an arteritis? There are no signs to point to an embolism from the heart.

In this connection let us look at the ECG and a teleradiogram of the chest. Well, the ECG (Fig. 1) shows a normal axis. The standard limb leads show slight depression of the S-T segments. The unipolar limb leads show nothing abnormal. I am only moderately impressed by the flat

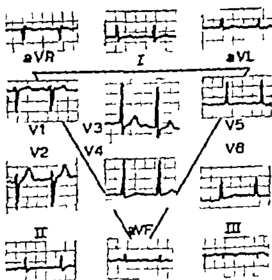


Fig. 1. Electrocardiogram recorded on Oct. 7, 1964.

S-T depression in Lead V_4, which is suggestive of subendocardial ischemia.

The teleradiogram of the chest taken in June is normal. In particular, the cardiac outline is normal, which makes me doubt the validity of my suspicion of coronary occlusion from the ECG because many people with ischemic heart disease have enlarged hearts, especially if they have been in cardiac failure. There is certainly no suggestion of mitral valve disease. The teleradiogram taken in October shows an opacity at the base of the right lung suggestive of a small pleural effusion or some collapse. These changes might be held to be consistent with pulmonary embolism or infarction. Incidentally, there is no radiologic evidence of interstitial edema or left atrial hypertension.

When this patient was first seen, were any of his pulses missing?

MR. ASHTON: I saw him first on September 30 when he presented with the vascular abnormalities described in the history. I have no record of his pulses before that date. To return to the question of a possible heart lesion, I should like to point out that there was some discussion of whether a diastolic murmur was heard on occasion in the mitral area.

PROF. GOODWIN: Was there any evidence of gallop rhythm?

MR. ASHTON: No.

PROF. GOODWIN: Well, I do not attach much importance to this murmur because there is no evidence of atrial fibrillation or subacute bacterial endocarditis. Even if a mitral diastolic murmur were heard, it does not guarantee that emboli would be present. I know that a short diastolic murmur of this type can be easily confused with a third heart sound in very sick people. Anyway, I am sure that if a mitral valve lesion were present which had precipitated thrombus formation and given rise to multiple systemic emboli, there would be no doubt as to the diagnosis of the mitral lesion.

To continue, he developed diarrhea with fresh blood in the stools. As a therapeutic cynic, I wonder whether the bleeding was due to the therapy! After all, if he did have emboli and was put on anticoagulants, the subsequent bleeding from lips and so on may have been due to sensitivity to phenindione. Less likely, this bleeding tendency may have been an expression of purpura due to thrombocytopenia or even a collagen disease.

His anuria may have been due to drug sensitivity or to some lesion of his renal arteries, such as dissection, arteritis, or embolus. The fact that a biopsy of the left gastrocnemius muscle was performed reveals that the clinicians were almost certainly considering a diagnosis of polyarteritis nodosa. But the story has important omissions for this to be seriously entertained. There was no history of hypertension, abdominal pain, or peripheral neuropathy.

Then, after a radiologic investigation, he felt faint and collapsed. This may well have been a coronary occlusion. Finally, he developed a left hemiplegia and died. Once again, both of these episodes suggest an acute vascular emergency due to embolus or dissection. To summarize, then, what is the nature of this vascular lesion that we are repeatedly referring to? Is it polyarteritis nodosa or some collagen disease akin to it? As I have said, the clinical picture is not really suggestive of this. It is a dissecting aneurysm? There is nothing definite enough in the history to indicate this. Is the whole thing due to multiple systemic emboli with subsequent sensitivity to phenindione? Possibly, but I can really find no evidence of a source for such emboli. This being the case, I must return to the idea of a primary arteritis giving rise to multiple bizarre lesions. Here again, though, such a disease would usually have a slower onset and there would be preceding general malaise, loss of weight, and even fever. The basilar artery insufficiency and pain behind the eye would fit in well with an arteritis.

What therapy did he receive? This will settle the problem as to whether he had vascular occlusion.

MR. ASHTON: He received heparin, phenindione, alcohol, and low molecular weight dextran (Rheomacrodex).

PROF. GOODWIN: This indicates that he was clearly considered to have vascular occlusion rather than dissection. What other investigations were performed?

MR. ASHTON: A barium meal and follow through after his bleeding from the gastro-

Table I. Hemoglobin and blood urea levels

Date	*Hb (Gm.)*	*Blood urea (mg.)*
June 18	93 (13.6)	
June 25	92 (13.3)	
October 1	81 (11.9)	41
October 8	60 (8.8)	134
October 9		181
October 10	58 (8.5)	228
October 12	58 (8.5)	387
October 13		402

Table II. Serum electrolytes (mEq./L.) in October 1964

Date	*Na*	*K*	*Cl*	*Standard HCO₃*	*pH*
October 1	130	5.1	101	25	7.33
October 8	127	4.0	92	20.8	7.37
October 9	122	4.7	90	19.8	7.37
October 10	119	5.0	86	19.8	7.45
October 12	122	4.6	87	14.3	7.28
October 13	122	4.3		13.1	7.25

intestinal tract. This was normal. The final investigations carried out during his terminal uremic phase were cystoscopy and retrograde pyelography. Cystoscopy revealed that the bladder and ureteric orifices were normal. There was no drainage of urine when the ureteric catheters were passed. The retrograde pyelograms were normal.

PROF. GOODWIN. Do we have knowledge of the levels of hemoglobin and blood urea?

MR. ASHTON. Yes. (See Tables I and II.)

PROF. GOODWIN. The first hemoglobin level is normal, but there is then a rapidly progressive anemia. These figures suggest that this fall is due to the episodes of bleeding. The blood urea levels reveal that something dramatic happened to the kidneys between October 1 and 8, probably infarction.

May we hear what the muscle biopsy showed?

DR. HEATH. The biopsy of the gastrocnemius muscle showed the features of infarction of muscle. In some microscopic fields there was very severe degeneration of muscle with almost total loss of fibers. In others there was evidence of sarcolemmal proliferation and muscle regeneration. The small arterioles and venules included in the biopsy were normal. In particular, there was no evidence of polyarteritis nodosa.

PROF. GOODWIN. Do you regard these changes as being indicative of ischemia and not related to any particular vascular disease?

DR. HEATH. Yes, they represent muscle degeneration and regeneration after occlusion of the arteries to the muscle. Incidentally, transaminase levels were estimated: the serum glutamic oxaloacetic transaminase level was 158 units (normal 15 to 40 units) and the serum glutamic pyruvic transaminase level was 43 units (normal 15 to 40 units). What do you think about these levels?

PROF. GOODWIN. They indicate necrosis of muscle, possibly myocardium and certainly striated muscle of the calf. Well, in spite of these vague reports of a mitral diastolic murmur and vague electrocardio-



Fig. 2. Left side of heart, showing myxoma situated on atrial wall above mitral valve.



Fig. 3. Atrial septum showing myxoma arising from rim of fossa ovalis. Hematoxylin and Van Gieson, X 4.5

graphic evidence of myocardial ischemia, I still think that we are dealing here with widespread vascular occlusion due to an arteritis, giving rise to the bizarre clinical presentation. Of course, we must bear in mind that a common disease like atherosclerosis may rarely give rise to bizarre signs.

DR. JONES. Can you absolutely exclude myxoma of the left atrium on the evidence that we have had?

PROF. GOODWIN. I cannot, but one diagnoses left atrial myxoma by a combination of signs which usually include those suggesting mitral stenosis. One may expect a loud third heart sound, a short mitral diastolic murmur and a loud widely split first sound. Signs of pulmonary hypertension are common but not invariable. Thirdly, there are the signs of general systemic disease such as anemia, loss of weight, fever and abnormal blood proteins. Finally, there are embolic phenomena.[1] In this case we have ample evidence consistent with emboli but only vague suggestions of mitral valve disease. In my experience, the murmurs in left atrial myxoma do not disappear completely. Rarely, I must admit that a cardiac myxoma is first diagnosed when emboli occur and the mass is removed by a surgeon; it is then sectioned by the pathologist who finds myxoma.

PROF. ARNOTT. I agree with Professor Goodwin that all the features of this case could be ascribed to thrombosis and embolism secondary to atherosclerosis which have presented in a bizarre fashion. I suspect, however, that our pathologists, knowing of Professor Goodwin's interests, have presented him with an atrial myxoma presenting in an obscure fashion.

DR. KAY. The major pathologic features were confined to the cardiovascular system.

The heart (370 grams) contained a soft, red, gelatinous, rather friable sessile polypoid tumor (5 cm. in diameter) which was attached to the wall of the left atrium about 2 cm. above the orifice of the mitral valve (Fig. 2). Microscopically, the tumor appeared to arise from the subendocardial connective tissue at the rim of the fossa ovalis (Fig. 3). It consisted of a mass of a faintly basophilic, vascular tissue containing few cells, covered by endothelium. The cells were elongated and round and possessed spherical or ovoid nuclei con-

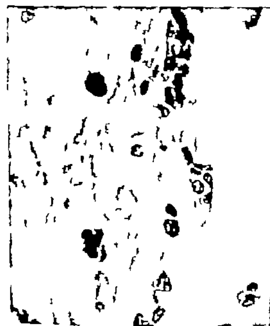


Fig. 4. Myxoma. Syncytial groups of cells in loose fibrillar stroma. Hematoxylin and Van Gieson, X150.



Fig. 5. A, Artery in gastrocnemius muscle occluded by myxoma. B, Adjacent muscle shows areas of regeneration after ischemic necrosis. Hematoxylin and eosin. ×135.



Fig. 6. Kidney. Arcuate artery containing myxoma embolus covered by endothelium. Hematoxylin and eosin. ×135.

taining prominent nucleoli. Occasional binucleate forms were present. Some groups of cells had poorly delineated cytoplasmic margins and appeared to form a syncytium (Fig. 4). No mitotic figures were seen. The stroma contained fine collagen and elastic fibers. Areas of the tumor matrix stained positively with the periodic acid Schiff (P.A.S.) reaction and with alcian blue, indicating a content of neutral and acid mucopolysaccharides. The stroma included several areas of old and recent hemorrhage.

The gross and microscopic appearances of the tumor were those of a primary cardiac myxoma.

The myocardium contained numerous foci of fibrosis and resolving infarction. Small radicles of the coronary arteries were occluded by myxomatous emboli. In one vessel the tumor was closely applied to the intimal lining and appeared to be invading the wall.

The proximal 5-cm. section of the right anterior tibial artery was occluded by a mass of soft red gelatinous material which on microscopic examination proved to be myxoma. Both gastrocnemius muscles were pale and soft. Microscopically, arteries in the intramuscular septa were occluded by myxomatous emboli and the muscles showed regenerative changes after ischemic necrosis (Fig. 5).

The spleen contained numerous recent infarcts and within the organ small arteries were occluded by emboli of myxoma.

The kidneys presented a "flea-bitten" appearance due to the presence of multiple recent cortical infarcts. Microscopic examination confirmed the nature of the infarcts and revealed emboli of myxoma in hilar arcuate (Fig. 6) and interlobular arteries. The cells of the proximal parts of the renal tubules were grossly swollen and showed a fine vacuolation of their cytoplasm. A similar change also affected the parietal cells of some of Bowman's capsules. These changes probably represent an osmotic nephrosis induced by the intravenous administration of low molecular weight dextran during the first 6 days after the patient's admission to hospital. They are similar to the changes described by Vickery[4] and are generally regarded as being transient in nature and not related to an impairment of renal function. The

apical portions of some of the proximal tubular cells also contained strongly eosinophilic intracytoplasmic hyaline droplets which stained intensely with the P.A.S. method.

The lungs showed a mild degree of pulmonary edema. The pulmonary arteries were microscopically normal

DR. SMITH Inspection of the fresh brain revealed a large area of recent hemorrhagic softening involving the anterior half of the right superior and inferior parietal lobules and the adjacent posterior edge of the postcentral gyrus. Section of the fixed brain showed that this softening (maximal size in coronal section 6 cm. vertically and 3 cm. laterally) extended forward into the white matter of the precentral gyrus and the corona radiata It no doubt accounted for the left hemiplegia which developed 4 days before death. Small infarcts (less than 1 cm in diameter) were also seen in the right caudate and amygdaloid nuclei and both thalami the dorsal surface of the left cerebellar hemisphere showed two irregular zones of necrosis which were mainly cortical.

Histology of the right frontoparietal softening confirmed its recent origin its cortical component showed marked capillary congestion, pericapillary hemorrhages necrosis and infiltration of capillary walls with polymorphonuclear neutrophils, ischemic homogenization of neurons, and associated spongiform degeneration the subjacent white matter was irregularly affected and showed pallor of myelin staining and early degeneration of myelin sheaths. The lesions in the left cerebellar hemisphere were similar and there were many comparable small recent lesions, varying from 0 1 to 1 0 cm in cross section distributed randomly throughout the frontal parietal, temporal and occipital cortices, amygdaloid thalamic, and caudate nuclei of both hemispheres, and the pons and medulla

In other areas, which included frontal and occipital cortices hippocampi pons, and medulla, there were small but older lesions measuring less than 0.5 cm. across, showing central retiform gliosis and variable degrees of infiltration with lipophages and siderophages and denser surrounding gliosis which included large gemistocytic



Fig 7 A Shows a small old infarct in the frontal cortex, surrounded by dense gliosis. Hematoxylin and eosin, X24. B (inset), Shows a small artery in the adjacent subarachnoid space containing adherent, endothelialized, partly organized myxoma embolus. Hematoxylin and eosin X30

astrocytes (Fig 7,A) Some of these older lesions in the brain stem were probably related to the presenting clinical features which Professor Goodwin considered to be suggestive of basilar artery insufficiency

Alongside some of the infarcts, small arteries in the subarachnoid space and also intracerebral arterioles contained emboli of myxoma and did not show superimposed thrombosis. However occasional emboli did show recanalization re-endothelialization, and limited fibrous obliteration (Fig 7,B)

The above-mentioned changes, therefore account for most of the neurological symptoms and signs As for the terrific ache behind the eye and the visual deterioration, I suspect that these symptoms could have been due to embolic occlusion of the ophthalmic artery or one of its retinal branches. Although retinal embolism is usually painless, cases have occasionally been reported in which this was not so[3] and retinal occlusion by atrial myxoma has been described on at least three occasions.[4]

DR. HEATH: There is much controversy as to the nature of atrial myxomas. Professor Goodwin, do you think they are atypical thrombi or true neoplasms? Professor Orr, if they are tumors, do you think that "myxoma" is the right description for them?

PROF. GOODWIN: I am sure that they are tumors, for they do not have the macroscopic or histologic features of degenerated thrombus. They can also be easily distinguished on angiocardiography. Furthermore, most patients with myxomas have systemic disturbances, such as malaise, loss of weight, and anemia, together with an increased sedimentation rate and nonspecific changes in the plasma proteins. These may be due to protein being squeezed into the blood stream and setting up an autoimmune reaction. It has been suggested that the myxoma acts as a mechanical erythrocyte-disintegrating machine. Against this hypothesis is the fact that clinical evidence of red cell destruction in the form of a hemolytic anemia has not been demonstrated. Patients with mitral valve disease and a large thrombus in the left atrium do not show these clinical features.

PROF. ORR: I agree that they are tumors. One of the interesting features is that they appear to prevent the formation and subsequent propagation of thrombus on their surfaces. They are not true myxomas because they do not consist of typical stellate myxoma cells. I have stated previously[1] that I believe that they are derived from endothelium or endocardium. Commonly these tumors include aggregations of lepidic cells.

I have not examined the sections from this particular case, but in previous examples that I have studied there have been tubular structures, and the view that I put forward at the time was that these tumors were endotheliomas. The mucin and polysaccharides in the tumor may be products of degeneration. I might say that this view has been severely challenged by Willis, but you can all read about that in this book![10]

DR. HEATH: I agree that atrial myxomas are true tumors and furthermore I believe that some of them exhibit a limited degree of invasiveness. Recently, Mackinnon and I studied a myxoma of the right atrium,[7] portions of which had broken off to give rise to multiple pulmonary emboli and pulmonary hypertension. We thought that this was an excellent opportunity of determining whether such atrial myxomas are thrombus or tumor, for if they are thrombi, emboli from them impacted in the pulmonary arteries would show organization and the characteristic features of pulmonary thromboembolism. In fact, when the portions of tumor impacted in the pulmonary arteries were studied, they showed histologic appearances suggestive of infiltration through the media and extension into the surrounding adventitia. Clearly, this suggests that the atrial myxoma is a true tumor that occasionally shows limited invasiveness.

PROF. GOODWIN: One of the most interesting clinical features of this case is the fact that there were no certain signs of obstruction of the mitral valve. I think that this is because the myxoma was unusually small in this case and did not hang down into the mitral valve orifice.

As regards invasiveness, removal of these tumors produces rapid clinical improvement, and the results of surgical treatment are good. One of our patients treated by this operation has been followed for 4 years and there is no evidence of recurrence. A cardiac bypass technique is employed, incorporating a special filter to catch any fragments that are released.

Some cases of myxoma are accompanied by finger clubbing. Was there any evidence of clubbing in this case?

DR. KAY: No. Incidentally, no gross lesion was found in the gastrointestinal tract to account for the bleeding from this site. I attribute the hemorrhage in the early part of the terminal illness to anticoagulant therapy, since the bleeding ceased promptly when anticoagulant drugs were withdrawn and the administration of intramuscular vitamin K_1 was instituted. It seems likely that the terminal hemorrhage was due to microscopic uremic gastric erosions.

DR. HEATH: In conclusion, then, we have seen an unusual case of left atrial myxoma giving rise to great difficulty in diagnosis since it presented neither signs of obstruction at the mitral valve orifice nor charac-

teristic systemic disturbances. It presented a bizarre clinical picture of multiple emboli to the calf muscles brain spleen kidneys, and heart It eventually led to the death of the patient by producing a massive cerebral infarct

Diagnosis Myxoma of the left atrium with multiple systemic emboli.

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Clinical problems of cardioversion

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Push button warfare has been declared on cardiac arrhythmias.[1-14] The new weapons have been made available before most physicians understand their operation or the indications for their use. Fortunately, in most situations there is little immediate harm that can come to the patient from the use of properly synchronized direct-current countershock. These new techniques are not a panacea for the management of cardiac arrhythmias and the purpose of this paper is to present some of the clinical problems *occurring just prior to, at the time of*, and *immediately after* cardioversion. The problems related to the drug prevention of the recurrence of cardiac arrhythmias after defibrillation are considerable and may present certain difficulties in the long range management of these patients, but are not included in the present paper.

Selection of patients

The selection of patients for electrical reversion is not a casual matter. In any individual patient, the dangers subsequent to reversion must be balanced against those of allowing the abnormal rhythm to continue.

Atrial fibrillation. In 1908 Sir James Mackenzie wrote concerning atrial fibrillation: "The most important of the continuous abnormal rhythms is that due to fibrillation of the auricles. . . . The great frequency of its occurrence renders it imperative that all practitioners should become familiar with its symptomatology, for 60 or 70 per cent of all cases of serious heart failure met with in practice owe the failure to this condition, or have the failure aggravated by its presence. . . ."[17]

Current opinion is little changed from these views of Mackenzie expressed half a century ago. In general, the availability of electrical countershock has extended the indications for reversion of this condition.

INDICATIONS FOR REVERSION OF ATRIAL FIBRILLATION. Reversion of atrial fibrillation is indicated in the following circumstances: (1) young or middle-aged patients, with or without heart disease or heart failure; (2) patients with hyperthyroidism in whom atrial fibrillation persists after the hyperthyroidism has been controlled; (3) patients with congestive heart failure in whom ordinary methods of therapy have not controlled the decompensation; (4) certain patients with angina pectoris which is not easily controlled by ordinary methods of treatment, whether congestive heart failure is or is not present; (5) patients with peripheral or pulmonary emboli thought to originate from the atria; (6) patients with atrial fibrillation in whom the

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ventricular rate cannot be controlled adequately with digitalis (7) patients in whom palpitation is very bothersome and (8) patients with intraventricular conduction disturbance or bundle branch block in whom there are indications for reversion (should be reverted by electrical means rather than by pharmacologic methods)

CONTRAINDICATIONS TO THE REVERSION OF ATRIAL FIBRILLATION Reversion is contraindicated in the following circumstances (1) patients who are unable to tolerate prophylactic agents such as quinidine because of idiosyncrasy hypersensitivity or cinchonism (2) patients in whom reversion has been accomplished several times without significant improvement in the patient's clinical status and in whom atrial fibrillation has recurred repeatedly despite adequate prophylactic therapy with quinidine and (3) patients with complete heart block.

RELATIVE CONTRAINDICATIONS TO THE REVERSION OF ATRIAL FIBRILLATION Reversion may not be necessary or may be relatively contraindicated in the following circumstances (1) Asymptomatic elderly patients in whom atrial fibrillation is easily controlled with digitalis may not require reversion. (2) Reversion should probably not be attempted in patients with atrial fibrillation who have extremely slow ventricular rates without digitalis therapy since the frequency of disease of the sinoatrial and A V nodes is high in this group and treacherous arrhythmias including sinoatrial block, slow A V nodal rhythm and sinoatrial standstill may occur at the time of reversion (3) Patients in whom atrial fibrillation has occurred as a result of digitalis toxicity or patients with atrial fibrillation who have other evidence of digitalis toxicity must be carefully evaluated prior to electrical reversion since more serious arrhythmias may be produced by reversion certain of these patients may need potassium therapy (4) In patients in whom mitral valve surgery is planned in the near future, reversion should not be attempted until after recovery from the operation [14]

In years past contraindications to the reversion of atrial fibrillation included long duration of the atrial fibrillation marked cardiac failure peripheral emboli and severe angina pectoris. It is interesting to note how many of these former contraindications are now considered to be indications for reversion

Ventricular fibrillation When the heart



Fig 3 Thirty-four-year-old woman who had cardiac arrest in the operating room at time of operation for diffuse nontoxic goiter Arrest occurred immediately after incision of the skin had been made and external massage was started as soon as lack of pulse was detected. Initial electrocardiogram showed ventricular fibrillation. One milligram of intracardiac epinephrine had been given, without results After the administration of 100 c.c of sodium bicarbonate given rapidly intravenously approximately 15 minutes after onset of ventricular fibrillation the rhythm spontaneously reverted to a normal sinus mechanism The pati[illegible] further complications.

has been properly conditioned this fatal arrhythmia usually can be eradicated. Experimental and clinical evidence has demonstrated that the heart becomes acidotic very rapidly after circulatory arrest.[illegible] The acidotic hypoxic myocardium will not respond to catecholamines or electrical shock[21]; therefore it is mandatory to establish an adequate airway, provide ventilation, begin external massage, and administer sodium bicarbonate (initially 44 to 88 mEq. in the adult) intravenously if the arrest has persisted more than 30 to 45 seconds. Once these steps have been carried out, electrical defibrillation is usually a simple matter. When arrest occurs in the operating room, these maneuvers will frequently restore normal rhythm without the necessity for electrical countershock. (See Fig. 1.)

For the electrical treatment of ventricular fibrillation, either an A.C. or D.C. defibrillator is adequate.[illegible] If repeated shocks are necessary, however, there is probably less myocardial damage with the D.C. defibrillator.[illegible]

Other arrhythmias. The need for the reversion of certain other arrhythmias which can be effectively eliminated by electrical shock, i.e., atrial flutter (Fig. 2), other supraventricular tachycardias (Fig. 3), or ventricular tachycardia (Fig. 4), is often more urgent than the need for the reversion of atrial fibrillation. If conventional therapy does not control these arrhythmias in a short period of time, electroshock under transient narcosis is usually indicated. Although electrical reversion has been reported to be successful in patients in whom these arrhythmias were produced by digitalis intoxication,[27] our own experience has been that digitalis-

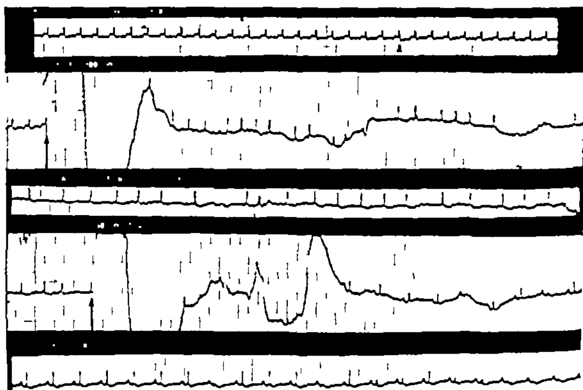


Fig. 2. Sixty-six year-old man admitted with atrial flutter. The patient was started on digitalis to slow ventricular response, but continued to have some pain of cardiac ischemia with 2:1 block. Six hours after admission, he developed typical signs and symptoms of acute appendicitis. Electrical reversion at 100 watt-seconds resulted in atrial fibrillation (*Lines 2 and 3*); therefore, countershock was repeated at 150 watt-seconds and the resultant rhythm was a normal sinus mechanism (*Lines 4 and 5*). This was associated with complete relief of the cardiac pain but no change in the abdominal complaints. Several hours later, the patient underwent successful appendectomy under general anesthesia, without complications or subsequent arrhythmias. Note the synchronization check (*arrow*) in *Line 1*. (Other arrows indicate CDC, capacitor-discharge countershock.)

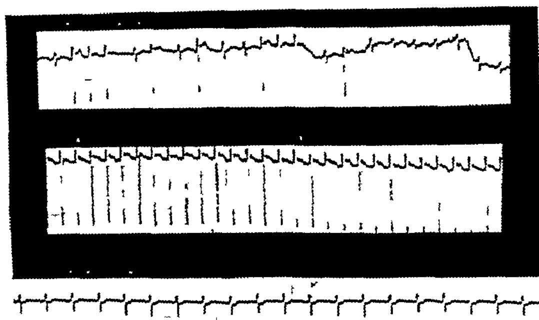


Fig. 3. Sixty-six-year-old man admitted with a history of palpitation occasionally associated with chest pain. The admission electrocardiogram revealed two atrial foci of pacemaker activity. The patient was started on digoxin, but 12 hours after admission, he developed the atrial tachycardia seen in Line 2. This rhythm persisted and was associated with pain of cardiac ischemia. Electrical reversion at 75 watt-seconds resulted in normal sinus mechanism (*Line 3*) and complete relief of pain. The patient was subsequently maintained on digoxin without recurrent episodes of arrhythmia.

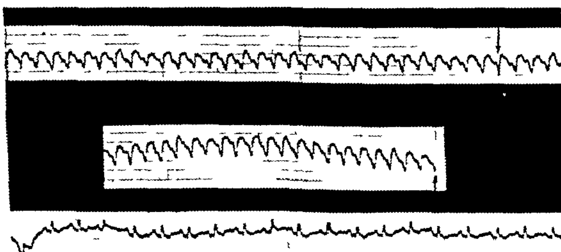


Fig. 4. Forty-two-year-old man with an acute anterior myocardial infarction. The patient developed ventricular tachycardia which did not respond to nasal oxygen or pressor agents. Procainamide (Pronestyl) 1 Gm. was given slowly intravenously without response. Electrical reversion (arrow at the end of Line 2 indicates the point at which the electrical discharge was released) was then performed under light Pentothal narcosis with immediate restoration of normal sinus rhythm. The cardiac pain associated with tachycardia disappeared, and the patient subsequently had a benign hospital course.

induced arrhythmias have usually either proved to be recalcitrant to countershock or been replaced by a less desirable rhythm after electrical reversion

Pharmacologic problems in cardioversion

The most frequently seen problem in patients undergoing electrical reversion is that related to drug therapy This is currently the greatest single factor in governing not only the incidence of arrhythmias at the time of reversion but also the probability that the patient will remain in sinus rhythm after reversion

Digitalis The accumulated experience of several groups with electrical reversion has led to the conclusion that the full amount of digitalis necessary for adequate control of the ventricular rate during atrial fibrillation may produce signs of digitalis intoxication after the rhythm has been reverted to a normal sinus mechanism[11,16] (See Figs 5 6 and 19) The omission of cardiac glycosides for several days prior to reversion will significantly reduce the occurrence of post shock arrhythmias Commonly the amount of digitalis necessary for maintenance therapy during sinus rhythm is less than was needed for adequate control of the ventricular rate during atrial fibrillation

It should be remembered that potassium increases the toxic effects of quinidine on the heart[35] and the use of potassium salts for digitalis intoxication may be hazardous in patients receiving maintenance quinidine after electrical reversion of cardiac

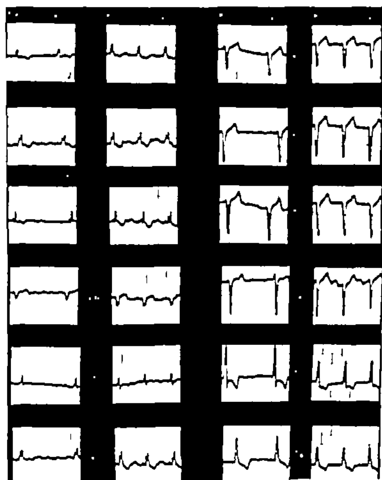


Fig 5 1 Fifty-nine-year-old man with hypertensive-arteriosclerotic heart disease and compensated congestive heart failure on maintenance digoxin 0.5 mg per day Prereversion and postreversion electrocardiograms recorded while patient was on maintenance digoxin

arrhythmias. If potassium therapy seems to be necessary, it has seemed to be prudent to also omit quinidine during this period until the arrhythmia has cleared, after which quinidine therapy may be reinstituted (Fig. 6).

Another problem encountered clinically has been observed in patients who have atrial flutter (Fig. 2) with a rapid ventricular response producing pain of cardiac ischemia, a clinical situation demanding immediate action. If the rhythm of these patients is electrically reverted prior to their receiving digitalis, the atrial flutter almost invariably returns within 15 to 20 seconds after the shock and reversion. On the other hand, if the patients first receive digitalis, even in a dosage which may not change the amount of A-V block, electrical reversion has been nearly 100 per cent effective in changing the atrial flutter to normal sinus rhythm.

Quinidine. Although quinidine is theoretically not the prototype of an ideal cardiac antiarrhythmic drug, it is certainly the best available at the present time. Other antiarrhythmic drugs, such as procainamide (Pronestyl) and antazoline (Antistine), are sometimes used; the former is much like quinidine in its action, and the latter drug has been withdrawn from possible commercial availability. Therefore, this section will deal only with the use of quinidine.

Before the advent of electronic methods for terminating cardiac arrhythmias, the greatest hazard in the reversion of arrhythmias resulted from the toxic effects of quinidine.[11,31-42] The published mortality rates from quinidine reversion of arrhythmias averages about 3 to 4 per cent.[42] Consequently, quinidine has been avoided whenever possible in patients with severe myocardial disease, congestive heart failure, or severe angina pectoris.

The technique of electrical reversion

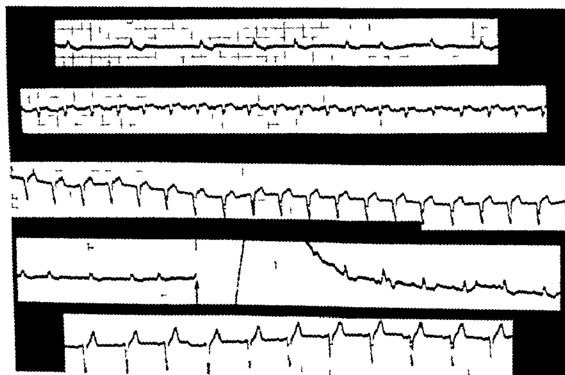


Fig. 5B. Same patient as in Fig. 5A. *Line 1.* Preshock rhythm before initial electrical reversion. *Line 2.* Development of paroxysmal atrial tachycardia with 2:1 block immediately after electrical reversion. *Line 3.* Lead V recorded 10 minutes after reversion, now demonstrating first-degree heart block. Patient subsequently returned to atrial fibrillation. *Line 4.* Repeat electrical reversion after digoxin had been discontinued for 3 days. (Arrow indicates CDC.) *Line 5.* Normal sinus rhythm after reversion.

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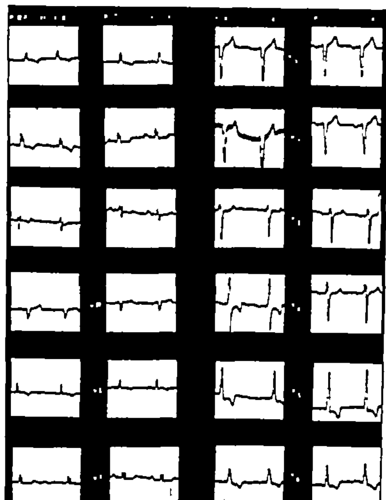


Fig. 5C. Same patient as in Figs. 5A and 5B. Preshock and postshock electrocardiograms in patient after being off digoxin for 3 days.

has not eradicated all of the hazards of quinidine therapy; conversely, it usually requires the exposure of severely diseased hearts to daily doses of this cardiac depressant.[8] However, the large doses sometimes used in the past for reversion are now no longer justified.[18]

Previous studies have shown that the incidence of sudden death is greater in patients treated with quinidine when there is associated congestive heart failure.[43] In our study of atrial fibrillation we have seen 7 cases of unexplained sudden death in patients who were still undergoing diagnostic evaluation before receiving quinidine. On the other hand, there have been 6 cases of sudden death in our patients on quinidine.[11] Two of these cases were documented to be ventricular fibrillation. One of these was most likely directly due to quinidine. But the other patient had other complicating factors. (See Fig. 20.)

Until a less toxic antiarrhythmic agent is produced, the physician must become expert in the use of quinidine and cognizant of its metabolism and early toxic effects.

Pharmacologically, quinidine and procainamide have five major effects: (1) depression of pacemaker impulse formation, (2) depression of atrioventricular and intraventricular conduction, (3) prolongation of the refractory periods of myocardial and conduction tissue, (4) depression of myocardial contractility, and (5) peripheral vasodilatation.[44]

Conn and Luchi[45] concluded that the cells of the conduction system are usually

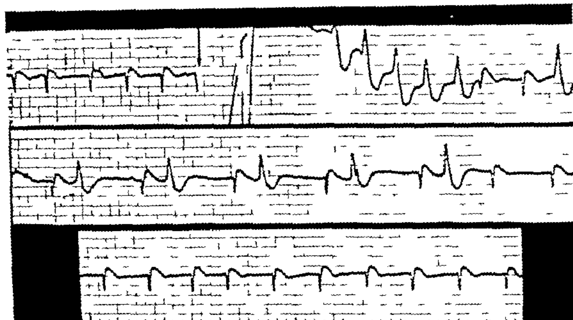


Fig. 6A. Sixty-three-year-old woman with rheumatic heart disease, mitral stenosis and regurgitation, chronic congestive heart failure, and atrial fibrillation. Continuous rhythm strip following CDC (capacitor-discharge countershock) in which there is initially a ventricular rhythm with evolvement to bigeminy and subsequently normal sinus rhythm. (Arrow indicates CDC.)

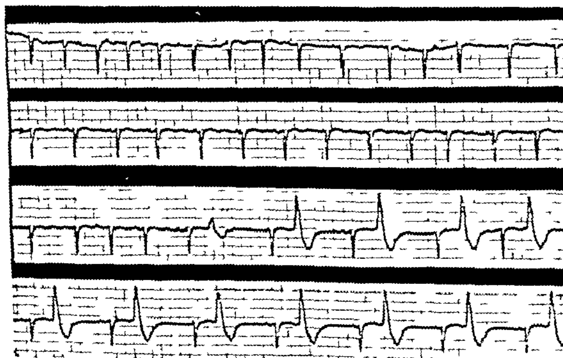


Fig. 6B. Same patient as in Fig. 6A. Lead V[illegible] recorded [illegible] minutes after CDC showing A-V dissociation and subsequently bigeminy with hypoventilation. Omission of digitalis and quinidine with supplemental potassium chloride resulted in normal sinus rhythm 36 hours later. Maintenance digitalis and [illegible] were [illegible] at that time.

more affected than muscular cells and that abnormal (ectopic) pacemaker tissue may be more sensitive to quinidine than *normal pacemaker tissue*.

After the oral administration of quinidine, the ratio of serum to myocardial quinidine concentration at equilibrium is about 1:10.[33] The sudden increase in the ratio of serum to myocardial quinidine concentration after intravenous administration of the drug may be responsible for some of the dangerous toxic effects encountered with this route of administration.[34]

The liver is the only tissue demonstrated to be active in the degradation of quinidine. Renal excretion is normally fairly rapid, and 10 to 50 per cent of a given dose of quinidine can be recovered unchanged in the urine within 24 hours after its administration to patients with normal renal function. Under normal circumstances, the serum half life of quinidine is approximately 2 hours.[1]

In individual patients, there is a considerable quantitative variation in the excretory rate which is related to the state of liver, renal, and circulatory function. *In patients with congestive heart failure*, quinidine and procainamide are more slowly excreted than in normal subjects.[41]

It is usually stated that the optimum serum level of quinidine for antiarrhythmic effects is between 2 and 8 mg. per liter.[33] Concentrations less than 2 mg. per liter are usually ineffective, whereas concentrations greater than 8 mg. per liter are associated with a very high incidence of toxic effects.[33] In patients with chronic congestive heart failure with decreased cardiac output or ischemia of the myocardium, the serum concentration resulting from oral administration of quinidine is less predictable because of decreased degradation and excretion.[41] Furthermore, a given amount of quinidine in the heart tissue may produce more cardiac toxicity when the myocardium is hypoxic.

In our recently published study of atrial fibrillation, almost 18 per cent of



Fig. 74. Fifty-two-year-old woman with rheumatic heart disease with mitral regurgitation, aortic insufficiency, and uncontrolled congestive heart failure. This patient normally had slow ventricular response to atrial fibrillation which did not increase after the omission of cardiac glycosides. Note the slow and erratic atrial pacemaker after electrical reversion at 100 watt-seconds. (Arrow indicates CDC.)

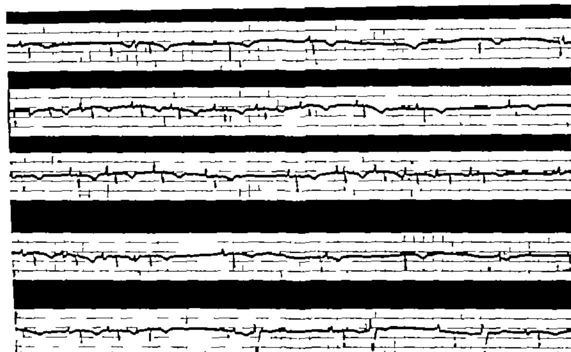


Fig. 7B. Same patient as in Fig. 7A. *Line 2.* An immediate but unsustained response to intravenous atropine with resumption of previous slow rate within 5 minutes. *Line 5.* Lead V after repeat administration of atropine intravenously.

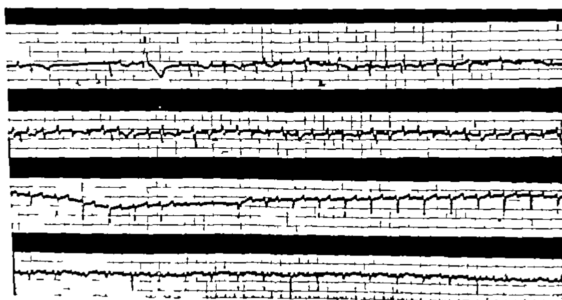


Fig. 7C. Same patient as in Figs. 7A and 7B. *Lines 1 and 2.* Two minutes after second injection of 0.5 mg. of atropine sulfate intravenously demonstrating development of atrial flutter. *Line 3,* Left carotid sinus massage. *Line 4.* Persistence of atrial flutter 12 hours after shock. Probably related to the increased ventricular response to atrial flutter the patient had a marked diuresis. The atrial flutter persisted for 10 days before returning to atrial fibrillation (again with drop in ventricular response to 50-60 beats per minute). Electrical reversion was repeated, with development of normal sinus rhythm.

149 patients receiving a total daily oral dose of only 0.8 Gm. of quinidine developed either severe cinchonism or overt toxicity to quinidine that required discontinuance of the drug. However, 97 per cent of the patients who were able to tolerate this dose of quinidine maintained normal sinus rhythm during the follow-up period of at least 3 months.[10]

It seems to be prudent to begin maintenance quinidine therapy for several days prior to electrical reversion for the following reasons: (1) to test the patient's sensitivity to this drug which must be continued after reversion, (2) to achieve a level of quinidine in the blood and heart in order to lessen the likelihood of relapse immediately after electrical reversion, and (3) to accomplish reversion in the small percentage (usually 10 to 15 per cent) of patients who require only this small amount for reversion to normal sinus rhythm.[2,10]

Atropine. Although one group of investigators has recommended the discontinuance of atropine-like drugs prior to electrical reversion,[43] we have not seen this problem in our series. On the other hand we have used atropine in the immediate postshock period for apparent pacemaker depression with severe bradycardia (see Figs. 7 and 8), usually with little or no results. At least one study has demonstrated a marked reduction in cardiac arrhythmias after EST (electroshock therapy) for psychiatric disorders by administering atropine prior to the electrical shock.[44]

Embolization

Embolism during chronic atrial fibrillation. Goldman[17] has stated that approximately 30 per cent of all subjects with chronic atrial fibrillation will eventually experience one or more serious pulmonary or systemic embolic episodes during the course of their atrial fibrillation. In one series of autopsies on 257 patients who had had atrial fibrillation, 42 per cent were



Fig. 8. Sixty-eight-year-old man with diffuse myocardial disease, chronic atrial fibrillation, and massive cardiomegaly. Note the slow erratic atrial pacemaker response in Lead V at 2 minutes after shock with only slight improvement 15 minutes after reversion. Atropine sulfate 1 mg. intravenously had no apparent effect. The patient gradually increased the response of the atrial pacemaker to normal rate within 24 hours. Digitalis and quinidine were discontinued until the normal rate returned. The arrows in Lines 1 and 2 indicate CDC.

found to have had one or more pulmonary or systemic emboli.[39] In patients operated on for acquired mitral valvular lesions 2.1 per cent (7 out of 335 cases) of patients in sinus rhythm had atrial thrombi, whereas 55.8 per cent (86 out of 154 cases) of patients with atrial fibrillation had atrial thrombi.[57]

Embolism associated with reversion. Rokseth and Storstein[19] reported two systemic emboli in 129 anticoagulated patients in whom reversion was effected with quinidine. Thomson[41] in a review of the literature reported four systemic embolisms after reversion in 137 patients treated with anticoagulants, as compared with 7 in 348 patients not so treated. In 186 reversions in 149 patients who received no anticoagulants, there were only two episodes of systemic embolism after reversion, even though 30.9 per cent of the patients had a history of previous pulmonary embolism and 7.4 per cent had a history of previous systemic embolism.[13]

Anticoagulants and incidence of embolism. The studies mentioned in the previous section and others would seem to suggest that anticoagulants do little in altering the incidence of postreversion embolic episodes. Studies reported have usually been made on patients anticoagulated from 10 days to 4 weeks prior to reversion and from 1 to 2 weeks afterward.[39,57] The risk of embolization reported[11,37,44] in these patients is the same as that found in patients not anticoagulated and reverted electrically, i.e., about 1 to 3 per cent.[2,7,22,33]

It has been suggested that chronic anticoagulation be carried out for atrial fibrillation. This is not feasible for at least two reasons. (1) Most patients are already fibrillating when first seen by the physician, and the duration may not be known. (Present anticoagulants do not dissolve preformed thrombi.) (2) Reports on large series of patients on long-term anticoagulants who are *adequately* anticoagulated[1] show that, despite all precautions, a significant number of patients develop some complications related to the anticoagulant.

The decision whether to employ anticoagulants will have to be answered for the individual patient on the basis of the emotional attitude of the physician.

Anesthesia

Anesthesia is an answer to the clinical problems of anxiety and hypoventilation.

Direct-current countershock is uncomfortable in the conscious patient. Most patients describe this sensation as an "explosion" in their chest, whereas others say that they experience instantaneous pain. Since the disagreeable sensation is only momentary, some investigators have elected to administer the electroshock without anesthesia. In this case, it is customary to administer some analgesic, such as meperidine (Demerol), in conjunction with a barbiturate such as pentobarbital (Nembutal) preceding the shock. This has the disadvantage of leaving the patient somewhat sedated after electrical reversion and may lead to *unrecognized hypoventilation* at a time when maximal oxygenation is mandatory. This possible disadvantage, along with the fact that this preshock medication fails to relieve the anxiety generated by multiple shocks, have caused most investigators to favor the use of "transient narcosis." This method has the following advantages: (1) The anxiety and discomfort produced by multiple shocks are reduced. (2) Small intravenous doses of thiopental sodium, 75 to 250 mg., produce rapid, adequate, and transient amnesia without the need for any additional sedative prior to the procedure. (3) The presence of an anesthesiologist helps to insure that ventilation will be adequate and that the heart will be maximally oxygenated.[13]

As a rule, the extent of skeletal muscle contraction during direct-current countershock is minimal, and muscle relaxants are not necessary. Furthermore, it should be remembered that parenteral quinidine may potentiate the paralytic effects of muscle relaxants.[9]

Problems at time of reversion

Technical problems related to electrical reversion. Several technical aspects should be stressed, since they may lead to annoying and sometimes hazardous problems.[14] The first of these concerns connection of the ECG monitor cables to the patient. It is mandatory that the monitor electrodes be placed on the extremities as far away from the defibrillating electrodes as possi-

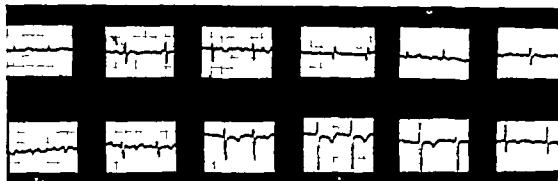


Fig. 9A. Fifty-year-old woman with rheumatic heart disease and mitral stenosis. The patient had developed severe exercise intolerance after the onset of atrial fibrillation 1 year previously. Electrocardiogram prior to reversion. Note the relatively low voltage probably secondary to the type of heart disease and the extreme obesity of this patient. Because of this and the coarseness of the fibrillatory waves it was impossible to get adequate synchronization. Therefore, one of the monitor leads was placed on the upper abdomen some 20 cm. from the defibrillating electrode.



Fig. 9B. Same patient as in Fig. 9A. Although CDC (capacitor-discharge countershock) was successful, a large electrical arc was produced above the patient and resulted in second-degree burns at the site of the monitor electrode on the abdomen. *Note the progressive change in the conduction pattern of the P waves before normal conduction is established.*

ble. (See Fig. 9.) Should the monitor electrodes be placed too near one of the defibrillating electrodes, the electrical current may arc from the defibrillator electrode *to the monitor electrode instead of* passing through the patient to the other defibrillator electrode. The arc which may thus be produced above the patient is an awesome spectacle and may produce severe skin burns at the site of the monitor electrode.

One should keep in mind that the electrical monitor-synchronizer system can be triggered by any impulse of sufficient amplitude and polarity. (See Fig. 10.) Therefore, the monitor lead that should be

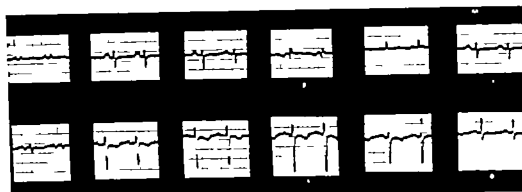


Fig. 9C Same patient as in Figs. 9A and 9B. Electrocardiogram after electrical reversion.

selected is one that has the greatest magnitude of QRS voltage in association with the least amplitude of the other components of the electrical cycle with the same polarity, i.e., P, T, or F waves. Once the synchronizer is set, the instrument should be test fired several times to assure correct triggering (Figs. 2, 4, and 10).

During the actual reversion, a continuous record may be obtained on a standard electrocardiograph machine via a special cable from the defibrillator. Some defibrillators have their own permanent recorder. When these continuous recordings are obtained, it is customary for the stylus to be thrown off the tracing momentarily. If the cardiac rhythm is irregular after the shock has been administered, an electrocardiogram is obtained to distinguish between atrial fibrillation and sinus rhythm with atrial

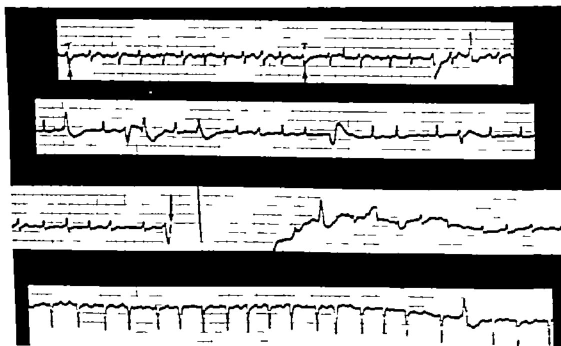


Fig. 10A. Seventy-one-year-old woman with arteriosclerotic heart disease, chronic atrial fibrillation, and chronic congestive heart failure with angina pectoris. There was no evidence of digitalis intoxication. Electrical discharge of 100 watt-seconds was triggered by ventricular ectopic contraction resulting in little change from previous rhythm. Arrows in Line 1 indicate test shocks. Arrow in Line 3 indicates CDC.

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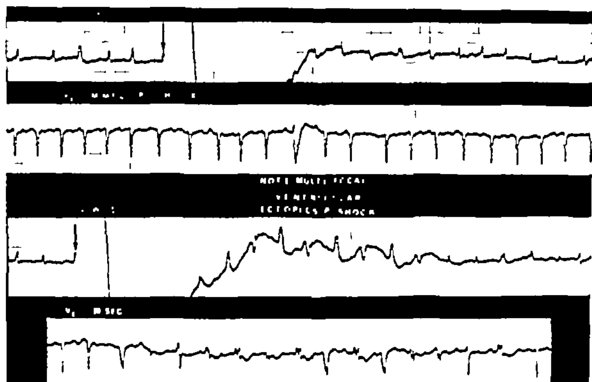


Fig. 10B Same patient as in Fig. 10A. Lines 1 and 2 Little change in rhythm by properly synchronized discharge of 200 watt-seconds. Lines 3 and 4 Evidence of increased ventricular excitability after discharge of 300 watt-seconds. Arrows indicate CDC.



Fig. 10C Same patient as in Figs. 10A and 10B. Line 1 Increased ventricular excitation after discharge of 400 watt-seconds (synchronizer triggered by ventricular ectopic contraction—*arrow*). *Line 2* Note the disappearance of increased excitability after 5 minutes. *Line 3* Note development of bigeminy with hypoventilation and its subsequent improvement *with more adequate ventilation (Line 4).*

or nodal ectopic beats. Lead V_1 is especially valuable for this purpose. Occasionally we have seen apparent atrial fibrillation persist for 5 to 10 seconds after the shock and then revert to normal sinus rhythm. The explanation for the latter peculiar phenomenon is not apparent.

Arrhythmic problems associated with electrical reversion. The individual variability immediately after reversion is considerable and a wide range of arrhythmias may appear before the sinus rhythm is established (Figs. 11, 12, and 13).[14] Ectopic atrial contractions and premature nodal contractions are very common immediately after electrical reversion of atrial arrhythmias. (See Figs. 14, 15, and 16.) Fortunately, these beats are usually of little consequence unless a premature ectopic atrial beat occurs during atrial repolarization, when excitation may produce resumption of atrial fibrillation (Fig. 17) or atrial flutter (Fig. 7C). During the first 15 minutes after reversion, a variety of other ar-



Fig. 11. Varying initial response of patients after capacitor discharge countershock. (Arrows indicate CDC.) *Line 1.* Forty-six-year-old patient with rheumatic heart disease and long-standing atrial fibrillation, moderately severe mitral stenosis, and mitral regurgitation. Probable sinoatrial block initially after reversion. *Line 2.* Fifty-eight-year-old woman with diffuse myocardial disease and 24-year history of atrial fibrillation. Idioventricular rhythm precedes re-establishment of atrial pacemaker. *Line 3.* Fifty-four-year-old man with paroxysmal tachycardia. Note that first visible complex after electrical shock has regular atrial pacemaker.

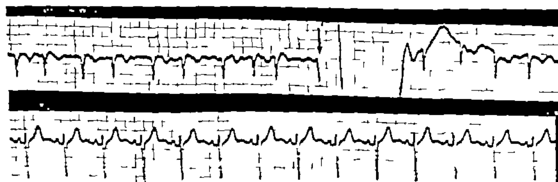


Fig. 12. Thirty-six-year-old man with rheumatic heart disease after commissurotomy. Although fibrillation had been present for several years, note the immediate development of regular pacemaker activity.

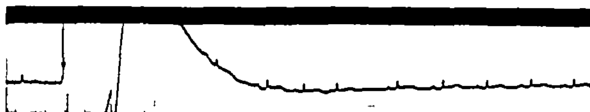


Fig. 13. Fifty-year-old man with rheumatic heart disease and mitral stenosis. Typical response after CDC (capacitor-discharge countershock), with occasional premature atrial contractions.



Fig. 14. Sixty-eight-year-old woman with ruptured papillary muscle and severe congestive heart failure. Note frequent ectopic contractions before the establishment of normal sinus rhythm. There was improvement in cardiac compensation but the patient later developed signs of quinidine intoxication.



Fig. 15. Seventy-three-year-old man with arteriosclerotic heart disease and moderately severe pulmonary emphysema. CDC (capacitor-discharge countershock) 100 watt-seconds resulted in sinus rhythm with premature atrial and premature nodal contractions. (Arrow indicates CDC.) *Lines 3 and 4*. Demonstrate development of intermittent nodal rhythm and frequent ventricular ectopic contractions. There was no evidence to suggest hypoventilation.

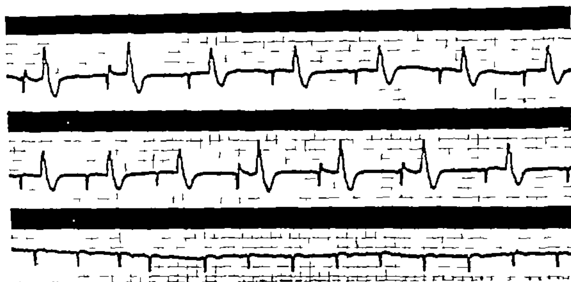


Fig. 15B. Same patient as in Fig. 15A. *Lines 1 and 2.* Wandering atrial pacemaker and ventricular bigeminy persist for some 20 minutes after reversion. *Line 3.* Lead V recorded 30 minutes after reversion when essentially only normal sinus rhythm is observed with occasional premature atrial contractions. These premature contractions persisted for 6 months after reversion.

Fig. 16. Seventy-three-year-old woman with aortic insufficiency probably secondary to rheumatic heart disease. The patient had unmanageable congestive heart failure. Note the similarity of Lead V after the initial unsuccessful electrical shock to the same lead after successful reversion. The occurrence of premature nodal contractions in the latter appear to have a similar counterpart in Lead V after the unsuccessful attempt. The patient had a marked diuresis after establishment of normal sinus rhythm.



Fig. 1. Twenty-eight-year-old woman with rheumatic heart disease and mitral stenosis. Commissurotomy 7 years prior to electrical reversion. CDC (capacitor-discharge countershock) at 100 watt-seconds results in normal rhythm until the occurrence of a premature atrial contraction (*see arrow Line 2*). CDC was repeated at 200 watt-seconds with similar result (*see arrow Line 4*).

Fig. 11. Sixty-three-year-old woman with Pickwickian syndrome and probable pulmonary hypertension. After reversion, the patient required constant stimulation to prevent recurrence of sleep and hypoventilation. When decreased ventilation occurred, the pacemaker would shift to the region of the A-V node but would return immediately to a normal mechanism after restoration of adequate ventilation. This phenomenon progressively became less evident as the effects of Pentothal were dissipated.

rhythmias and conduction disturbances may appear. In most patients in whom these have occurred, one of the following factors was thought to be responsible: (1) poor ventilation and oxygenation of the patient[31] (see Figs. 6B, 10C, and 18); (2) digitalis toxicity (see Figs. 5, 6, 19, and 21); or (3) hyperexcitability of the myocardium (see Figs. 8, 22, and 23) which at times appears to be induced by the electrical current, particularly when high-energy shocks are necessary. In the instances thought to represent post reversion hyperexcitability, the associated arrhythmia or conduction disturbance usually subsides in 5 to 10 minutes, leaving normal sinus rhythm, which may then either persist or occasionally revert to atrial fibrillation within the subsequent half hour. In this particular group of patients, if the rhythm relapses to atrial fibrillation, repeated shocks at the same or higher setting are not given since repeated shocks are likely to induce ventricular tachycardia or ventricular fibrillation.

After electrical reversion of any disturbance in rhythm, an occasional patient will have cardiac asystole. In 2 such patients, personally observed, immediate resuscitation was initiated and normal sinus rhythm commenced in less than 1 minute (Figs. 24 and 25).

We have noted that patients who have atrial fibrillation with a ventricular response of 60 beats per minute or less, with or without digitalis, prior to reversion have a much higher incidence of undesirable arrhythmias after reversion than do patients with a faster ventricular response. These disturbances in rhythm include sinoatrial standstill, with the supraventricular impulse originating in an ectopic atrial focus or from the atrioventricular node (Fig. 7), sinoatrial block (Fig. 11

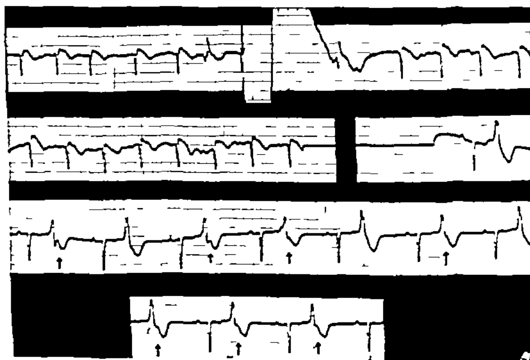


Fig. 19. Seventy-four-year-old woman who had atrial fibrillation secondary to thyrotoxicosis. The patient had a thyroidectomy in 1958, but atrial fibrillation had persisted, and at the time of reversion she was euthyroid. She had been maintained on digoxin after a pulmonary embolus several months prior to reversion. Note the difficulty in ascertaining the correct rhythm as seen on the monitor strip immediately after reversion (*Lines 1 and 2*). (Arrow in Line 1 indicates CDC.) Bigeminy developed in the short period of time required for recording Lead V. Omission of cardiac glycosides resulted in the resumption of normal sinus rhythm 36 hours. Arrows in Lines 3 and 4 indicate P wave buried in T waves of ectopic contraction.

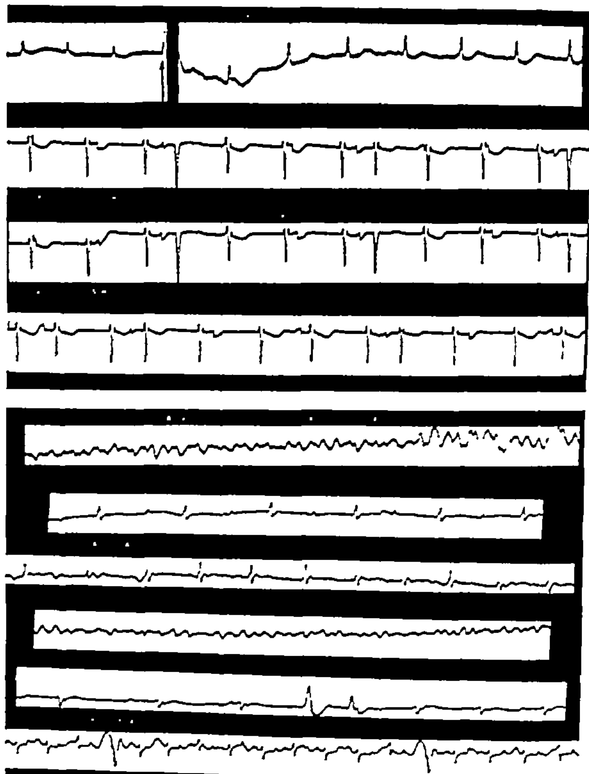


Fig. 20A. Sixty-year-old man with inoperable rheumatic heart disease with aortic stenosis, aortic insufficiency, mitral stenosis, mitral regurgitation, severe pulmonary hypertension, unmanageable congestive heart failure and CO_2 narcosis (venous CO of 5 mEq per liter at time of reversion). Nodal rhythm, A-V dissociation with occasional atrial capture after CDC (*capacitor-discharge countershock*) (*arrow—Line 1*).

Fig. 20B. Same patient as in Fig. 20A. Ventricular fibrillation after respiratory arrest some 12 hours after defibrillation. Note that slow ventricular response after AC defibrillation speed up with improved ventilation on two occasions. The patient subsequently died some 18 hours after CDC. Autopsy findings were compatible with the degree of disease mentioned (Fig. 20.1). The atria were enlarged, especially the left atrium, but no evidence of intracardiac thrombus formation was noted. The cause of the arrhythmia could not be determined but the respiratory difficulty, digitalis intoxication, or quinidine intoxication, separately or in combination, may have been responsible. Quinidine and digitalis were discontinued after reversion because of the immediate postshock rhythm.

Line 1) and slow A V nodal rhythm (Fig 20)

Advisability of repeated reversions

The advisability of repeated reversion should be determined on an individual basis, irrespective of the underlying disease process. Patients in whom there is noticeable improvement after reversion[14,20] and in whom deterioration develops when atrial fibrillation recurs, should have electrical reversion repeated as often as necessary. Even though in our series to the present time reversion has been effected in over 200 patients, a satisfactory means has not evolved by which we can accurately predict the degree of improvement in cardiac function which will be produced by the reversion of atrial fibrillation.[14] One should keep in mind that restoration of effective mechanical function of the atria may be delayed after restoration of normal sinus

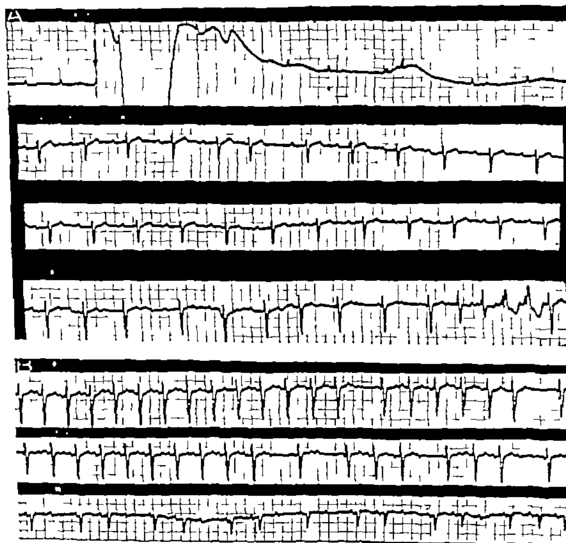


Fig. 21. Seventy-seven-year-old man with syphilitic heart disease and severe aortic regurgitation. This patient had uncontrolled congestive heart failure. *A*. There is a slow ventricular response after CDC (capacitor-discharge countershock) at 100 watt-seconds. Lead V. Immediately after electrical reversion show first-degree heart block and occasional premature nodal contractions (*Line 2*). Ten minutes after reversion (*Line 4* of *A* and *Line 1* of *B*), the patient developed an atrial tachycardia with varying block. Omission of digitalis and quinidine resulted in the disappearance of the atrial tachycardia and the establishment of a normal sinus mechanism some 24 hours later.

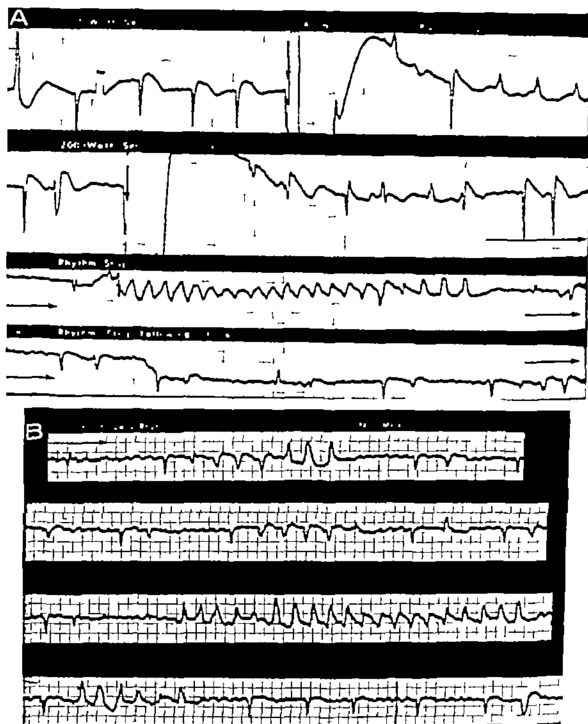


Fig. 22 Seventy-four year-old woman with arteriosclerotic heart disease and chronic congestive heart failure admitted to the hospital for symptoms and electrocardiographic findings suggestive of digitalis intoxication. The patient had been off digoxin for 18 days at the time of electrical reversion. *A. Line 1.* Demonstrates probable ventricular rhythm after CDC (capacitor-discharge countershock—*arrow*) at 100 watt-seconds. *Line 2. Evidence of increased* excitability after discharge of 200 watt-seconds (*arrow*). *Lines 3 and 4* in *A* and *Lines 1-4* in *B*. Continuous rhythm strip of lead V after the second electrical discharge (200 watt-seconds) revealed development of ventricular tachycardia, at times bidirectional. There was adequate ventilation during this period. No further attempts at reversion were made, and there were no further arrhythmias.

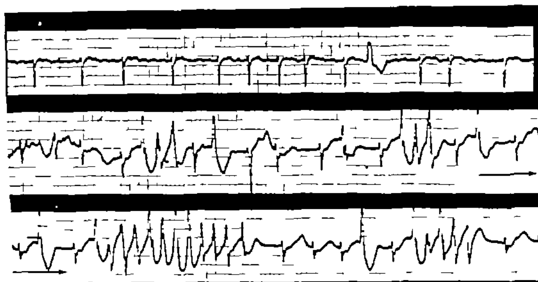


Fig. 23.1 Seventy-three-year-old woman with hypertensive-arteriosclerotic heart disease. Duration of atrial fibrillation at time of reversion was 3 years. Congestive failure had been well controlled with digitalis leaf (100 mg. per day), and the patient had no signs of digitalis intoxication at the time of reversion. There had been an increase in the frequency of angina pectoris during the previous 3 months. *Line 1*, The rhythm prior to reversion. The same lead immediately after the initial shock at 100 watt-seconds shows quite marked ventricular excitability (*Line 2*). This hyperexcitability persisted, as seen in Line 3, for 5 minutes after electrical shock.

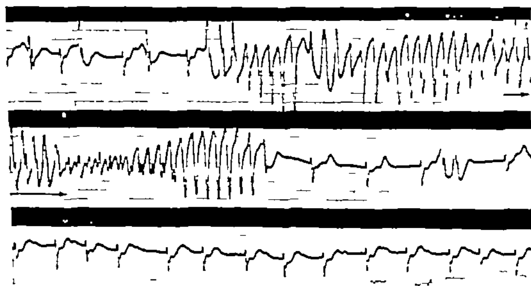


Fig. 23B Same patient as in Fig. 23.1. Lines 1 and 2 show the development of a biventricular tachycardia and a short burst of ventricular flutter. These arrhythmias were associated with a transient loss of the peripheral pulse. Adequate ventilation and oxygenation had been maintained by the anesthesiologist, and the patient was awake and fully reactive at the time of this last episode. As noted in Line 2, this arrhythmia spontaneously reverted to its previous state, and 30 minutes after CDC (capacitor-discharge countershock) the original rhythm had returned, and the patient was asymptomatic. The ischemic changes seen in Line 3 subsequently disappeared, and the patient had no further complications. There have been no further attempts at electrical reversion.



Fig. 24. Sixty-two-year-old man with arteriosclerotic heart disease and angina pectoris. Cardiac asystole after electrical reversion. External massage was followed by resumption of normal sinus rhythm, which has persisted now for 18 months. There has been no further episodes of angina pectoris.

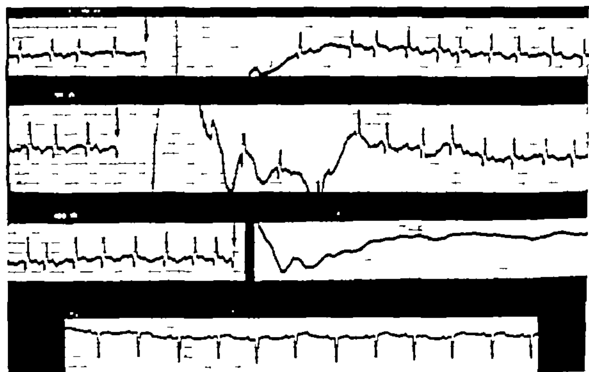


Fig. 25. Sixty-eight-year-old man with severe congestive heart failure secondary to hypertensive and arteriosclerotic heart disease. Heart failure had progressively become more difficult to manage since the onset of atrial fibrillation 1 year previously. There was no effect on the rhythm with 100, 200, or 300 watt-second discharges. (Arrows indicate CDC.) As noted above, there was cardiac asystole after the properly synchronized discharge at 400 watt-seconds. A sharp blow on the precordium resulted in resumption of normal sinus rhythm. The patient had marked diuresis after reversion and has maintained excellent cardiac compensation with sinus rhythm.

rhythm. Accordingly, the beneficial hemodynamic effects of reversion may not be immediately present.[14]

In our experience, as well as that of others,[9,22,23] patients with severe mitral regurgitation do not maintain sinus rhythm as often as do other groups of patients. In our experience, however, some patients with this entity have had marked improvement in cardiac function after electrical reversion; these patients deserve repeated reversion even if the normal rhythm persists for less than 3 to 4 months. In some patients in this category, we have noted a progressive decrease in the radiologic size of the atria after successive electrical reversion. Usually, these patients are immediately aware of their reversion to

atrial fibrillation and often they go rapidly back into cardiac decompensation.

Many Class IV cardiac patients have become Class II after reversion of atrial fibrillation. Similar findings have been reported by others.[12,21-23] We have had several patients who initially had unmanageable congestive heart failure for which they underwent electrical reversion, with marked lessening of the heart failure. Some of these did not develop significant heart failure when they relapsed into atrial fibrillation after 1 or 2 months of normal sinus rhythm.

Patients with angina pectoris made worse by atrial fibrillation may have complete disappearance of this symptom while in sinus rhythm. In some patients the return of atrial fibrillation has been associated with the recurrence of angina pectoris, even though the patients were not cognizant of the return of their arrhythmia.

Summary

Capacitor-discharge countershock offers the physician an effective and even dramatic tool in the treatment of many cardiac arrhythmias. It is not intended to be a substitute for sound clinical judgment or to be a "magic button" with which a cure may be effected

Some of the immediate problems associated with the clinical use of this form of treatment for certain cardiac arrhythmias have been discussed in order to emphasize its practical advantages as well as its limitations. We have not discussed the problem associated with the use of long term drug prophylaxis in maintaining normal rhythm once it is established

The push button technique of reversion should not be withheld as a fearful ultimate weapon in the war on cardiac arrhythmias, used only when all else has failed but as a safe effective instrument with which the physician may restore peace to the heart

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even more than the sum of the effects of the two drugs given singly. It is postulated that the tendency of DPH to deplete the intracellular sodium as well as the tendency of DCA to elevate the extracellular sodium act to increase the ratio of extracellular to intracellular sodium concentration, thereby stabilizing the cell membrane at a higher threshold.

Use in experimental arrhythmias. An early experimental study tested the premise that the area surrounding an acute myocardial infarction, the potential source of ectopic arrhythmias, being similar to the area of hyperexcitability surrounding an epileptogenic focus in the cerebrum, might be suppressed by DPH. By occlusion of a ramus of the left coronary artery in dogs, ventricular tachycardia could be predictably produced after a latent period of from 4½ to 8 hours. It was noted that when intravenous DPH was given during the latent period, the frequency of ventricular premature contractions was markedly decreased, and that when ventricular tachycardia occurred, doses of DPH in the range of 125 to 200 mg. per kilogram produced rapid conversion of the tachycardia, which recurred after brief periods. Further doses of the drug produced prolonged suppression of the arrhythmia. Orally administered doses produced the same effect, but with a delay in the onset of action.

The prevention of the onset of ventricular tachycardia in dogs made toxic with ouabain has also been reported. Dogs were given ouabain until the onset of ventricular tachycardia. While 10 per cent glucose showed no effect, DPH caused reversion to normal rhythm. Similar good results were obtained with procaine, procainamide, and quinidine, but the incidence of side effects and mortality was greater with these agents.

Aconitine and delphinine, applied directly to the atria, produces atrial flutter or fibrillation by increasing vagal tone. Although the effects of the two drugs may be abolished with atropine or by the local application of cold, quinidine and other antiarrhythmic agents have generally been unsuccessful in the treatment of the arrhythmias so produced. When, in another study, a dose of DPH, 5 mg. per kilogram, was infused into dogs with flutter or fibrillation induced by aconitine and delphinine, the arrhythmia stopped abruptly in all of the dogs treated with aconitine and in 6 of 8 of the dogs treated with delphinine. In the other 2 dogs the atrial rate gradually slowed until regular sinus rhythm was resumed. In most cases the arrhythmia disappeared within 2 minutes, the shortest period of time being 10 seconds after the infusion of DPH. In all cases the arrhythmia recurred from 2 to 14 minutes after the single dose. Injections of DPH were repeated in the same animal up to five times, with the same result in each instance. No dilation or weakening of myocardial contractility was observed in these dogs.

Clinical experience. In 1958, the successful clinical use of DPH for ventricular tachycardia was first reported in a woman who had received procainamide and quinidine without success. Procainamide was discontinued when the QRS group widened after the intravenous infusion of 2,300 mg. The patient was in extremis when 250 mg. of DPH was given intravenously. Within 2 minutes a sinus mechanism with atrial bigeminy was re-established and lasted for 20 minutes. The arrhythmia was successfully repressed with further doses at intervals of 4 to 6 hours.

It was not until early 1965 that two large series describing the clinical use of diphenylhydantoin appeared. In one series, the drug was administered as initial therapy intravenously for acute arrhythmias. An initial dose of 250 mg. was given over a period of 1 to 3 minutes with electrocardiographic monitoring, and repeated every 5 to 10 minutes until an effect could be established. When there was a change toward normal, the patient was observed for recurrence of the arrhythmia, in which event additional doses were given. After the response was firmly established, the patient was placed on maintenance doses of 300 to 400 mg. orally daily until resolution of the problem or until other drug therapy was established.

The cases described included 12 patients with arrhythmias suspected of being secondary to digitalis toxicity and 14 in whom there was no prior history of digitalis administration. Among the patients

with digitalis-induced arrhythmias, only 1 with atrial flutter did not respond whereas 2 with paroxysmal atrial tachycardia 1 with a complex atrioventricular rhythm 1 with paroxysmal atrial tachycardia (PAT) with wandering pacemaker 2 with ventricular bigeminy and 4 with multifocal ventricular premature contractions all responded promptly In one of the patients with PAT the response was an increase in block rather than a reversion to sinus rhythm Among the other patients responses were achieved in 2 cases of atrial tachycardia after cardioversion 2 cases of ventricular bigeminy 2 cases of multifocal ventricular premature contractions, and a single case of ventricular tachycardia In 2 patients with atrial flutter 2 with atrial fibrillation 1 with ventricular bigeminy and 1 with atrial tachycardia secondary to severe electrolyte imbalance there was no response. All responses occurred within 30 seconds to 4 minutes, or not at all Duration of response varied from 5 minutes to 4 to 6 hours

A second series gives the results of the oral use of DPH in patients with recurrent arrhythmias who had had inadequate response to conventional modes of therapy Conventional doses of oral DPH were used Of 37 patients with frequent ventricular premature contractions, 26 maintained regular sinus rhythm for an average of 16 7 months, 7 had a significant decrease in the number of ventricular premature contractions, and 4 showed no response Ten of 13 patients with paroxysmal atrial tachycardia were maintained in regular sinus rhythm without evidence of recurrence for an average of 18 months, 2 had some decrease in the frequency of paroxysms, and 1 showed no response All of 6 patients with atrial fibrillation showed no recurrences for an average of 13 months. Two patients with frequent atrial premature contractions and 1 patient with frequent A V nodal premature contractions had no recurrences, for an average of 19 months in the first 2 patients and for 16 months in the other patient One treated patient with atrial flutter had no response

Both of these studies should be considered to be preliminary because there were no control cases and comparison with other modes of treatment was largely inferential They do suggest however that DPH may have some beneficial effect on cardiac arrhythmias.

Toxicity Original early studies on the toxic side effects of DPH in laboratory animals showed that large doses were tolerated and that no histologic changes were noted in animals receiving ten times the clinical dose for a period of 6 months. In early studies, large doses of DPH or rapid injection intravenously occasionally produced respiratory arrest but with conventional doses, or when given over a few minutes, this is not a problem

The various toxic and hypersensitivity manifestations of DPH have been covered exhaustively in the literature encompassing extensive numbers of patients on long term therapy for neurological problems and need not be repeated here. Among the patients treated for cardiac arrhythmias in the two series discussed above, toxic manifestations were as follows skin reactions varying from urticaria to purpura drowsiness depression or nervousness, arthralgias, gingival hypertrophy and transient eosinophilia. Among those receiving the medication intravenously there was transient hypotension in 1 patient, and block with bradycardia in 1 patient All responded to cessation of therapy and supportive measures.

Conclusions The electrophysiologic evidence that diphenylhydantoin stabilizes cell membranes, the controlled animal studies showing a favorable effect on some arrhythmias, and the preliminary clinical studies suggesting its effectiveness in the arrhythmias of patients warrant further controlled studies of the range and consistency of action of diphenylhydantoin and of its value in comparison to established treatment Until these studies are done it should probably not be used as initial therapy for any arrhythmia In view of the drug's relative safety however employment of it in clinical situations in which other drugs have been ineffective does not appear to be unreasonable at this time

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Annotations

The cardiac impulse during ventricular systole

Cardiographic, angiocardiographic, and anatomic studies

Apex cardiography was one of the earliest methods of graphic recording of the heartbeat. With the advent of electrocardiography, phonocardiography, cardiac catheterization, and angiocardiography, interest in the apex cardiogram naturally waned since more accurate and fuller information was supplied by those techniques. Nonetheless, palpation of the cardiac impulse remains an important part of clinical examination of the heart and yields information which, taken in conjunction with other physical signs, helps to mold our clinical diagnosis at the bedside. For this reason, there has recently been a revival of interest in the recording of the cardiac impulse.

Methods of recording the impulse. The methods are divisible into two main types: the first records relative displacement of a localized area of the chest wall in relation to the surrounding chest wall,[1-4] and the second records absolute displacement in relation to a fixed point in space. The first method provides the traditional apex cardiogram. It is useful as a timer for mechanical events throughout the cardiac cycle, especially during the diastolic portion. The second method, that of recording absolute displacement, is known either as kinetocardiography or, as we prefer to call it, "impulse cardiography." This method is of special value in providing an optical record of what the hand feels when placed on the chest wall.

Relationship of areas on the chest wall to the ventricular cavities. Using the impulse cardiogram, Dellyannis and associates[5] have examined the impulses both at the apex and at the left sternal edge in health and disease. Angiocardiographic studies have shown that the apical impulse usually reflects movements of the left ventricle, whereas the left parasternal impulse reflects those of the right ventricle. In exceptional cases, however, with great hypertrophy of the right or the left ventricle this law no longer holds, for either ventricle may enlarge to such a degree as to underlie both areas of the precordium.

Types of impulse. Qualitatively four main types of impulses during ventricular systole have been noted: the normal, the overacting, the sustained, and the retracting.[5] The *normal* impulse moves outward for a period at the beginning of ventricular systole, always returning again to the base line before the last third of systole. In some cases actual retraction of the impulse occurs during late systole. The pattern of normal impulse is similar at both the apex and the left sternal edge. The *overacting* impulse is one of normal form but of abnormally large amplitude. It is typically seen in overacting hearts, as in the case of thyrotoxicosis or anxiety, but it is also related to the build of the chest, being often found in children and also in adults with a depressed sternum. Another example of an overacting impulse, confined to the left sternal edge, is that due to atrial septal defect, wherein the output of the right ventricle may be double or treble that of the left. The third type of impulse is the *sustained* impulse seen in the presence of hypertrophy of either ventricle or in cardiac aneurysm. This is the type of impulse usually described as "heaving" or "lifting." Although usually of greater excursion than normal, this need not necessarily be so: the basic abnormality independent of chest build is its sustained nature. In the impulse record the sustained outward movement continues into the last third of systole, often only returning to the base line in early diastole at the completion of the period of isometric relaxation. The fourth type, the *retracting* impulse, is seen in constrictive pericarditis, tricuspid incompetence, or with extensive pleuropericardial adhesions.

In defining these four types of impulse it is important to emphasize that these criteria apply when the patient is examined lying straight back on a couch or bed at an angle of about 45 degrees. Assumption of the left lateral decubitus position deforms the pattern of the impulse because of diaphragmatic and mediastinal shift.

Genesis of the apical impulse

ANGIOCARDIOGRAPHIC STUDIES. Timed angiocardiographic studies have shown that the basic difference between the normal impulse and the sustained impulse is mirrored in the movement of the portion of the heart underlying the apex beat. Thus, in health the anterior wall of the left ventricle near the apex of the heart moves initially outward in early systole and then retracts from the anterior chest wall, as the whole heart contracts concentrically during later systole. In left ventricular hypertrophy, however, the anterior wall of the left ventricle fails to retract normally from the anterior chest wall during the last third of systole, thus accounting for the prolonged sustained outward impulse.

ANATOMIC STUDIES. Studies of the different muscle layers of the heart (external spiral, middle circular, and internal spiral) suggested one explanation for failure of the apical portion of the heart to

in late systole in left ventricular hypertrophy. In health external and internal spiral fibers retract the apex, whereas the basal portion is squeezed by middle circular fibers which do not extend to the apex. In left ventricular hypertrophy, however, the middle circular fibers were found to extend to the apex and must thus tend to oppose the retracting action of the external and internal spiral layers; hence in systole the whole heart is squeezed and *little retraction of the apex takes place.* Other factors, however, probably also contribute to the genesis of the sustained impulse, including general increase in heart size and, in some cases, dilatation as well as hypertrophy.

Impulse cardiography aims eventually at producing a graphic record of palpatory physical signs in the heart and thus offers a more accurate and objective record of an important bedside physical sign.

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Cerebrovascular accidents in women taking oral contraceptives

In 1961, Jordan was first to report a case of thromboembolism in association with the administration of norethynodrel. The patient, a 40-year-old woman, had a pulmonary embolus. At a subsequent conference held in Chicago in September, 1962, to discuss the incidence of thromboembolic phenomena in women taking Enovid (norethynodrel plus ethynylestradiol 3-methyl ether), 132 case histories were presented. Two of these related to cerebrovascular incidents. The first (Case No. 10) was that of a 33-year-old woman who had been taking Enovid for 1 month and who developed a right hemiparesis and hemianopia. She improved gradually, but the right hemianopia persisted. The second patient (Case No. 20, age not given) had a normal delivery in October, 1961, and started on Enovid in December, 1961. In April, 1962, she suddenly developed a right hemiplegia and was aphasic. Carotid angiograms were normal. She had had rheumatic fever at the age of 10 years and had residual mitral insufficiency. She made a good recovery from her "stroke." The general conclusion of the conference was that there was no increase in the incidence of thromboembolic phenomena from the use of Enovid.

However, reports of additional cases of thromboembolic episodes associated with norethynodrel continued to appear, including the report of a case of nonfatal anterior cardiac infarction in a 32-year-old woman[1] and a case of left popliteal artery thrombosis requiring amputation in a 39-year-old woman.[2]

Zilkha[3] reported two cases of cerebrovascular accident in young women taking oral contraceptives. One was 25 years old and had a sudden onset of difficulty in speech and weakness of the right side of the face and right arm. Her blood pressure was 120/80 mm. Hg, and a left carotid arteriogram and an air encephalogram were both normal. An electroencephalogram confirmed the clinical impression of an acute lesion in the left frontotemporal region. She had been taking Enovid cyclically for 6 weeks. She gradually recovered over the succeeding months. The second case was that of a 26-year-old woman who complained of a disturbance of vision on waking one morning. Examination revealed a congruous left upper quadrantic field defect. There were no other abnormal physical signs. She had been taking norethisterone cyclically for 6 months.

Similar reports followed. Stewart Wallace[4] described two cases of acute ischemic episodes in the brain stem. The first case was that of 32-year-old woman who had been taking oral contraceptives for 22 months, and who suddenly developed severe vertigo, vomiting, ataxia, diplopia, right Horner's

syndrome, and loss of sensation over the right side of the face and the left side of the body. It was thought that she had had an ischemic episode in the territory of the posterior inferior cerebellar artery. She improved gradually. The second patient was 46 years old and had been taking the pill for 6 months. She had a sudden onset of vertigo and unsteadiness with lurching and a tendency to fall to the right. She also had visual discomfort and excessive drowsiness. Both plantar responses were extensor. She improved gradually.

Baines[2] reported the case of a 29-year-old woman who died from thrombosis of the left middle cerebral and right anterior cerebral artery. No source for an embolus was found at necropsy. She had been taking norethynodrel for 2 weeks only.

As pointed out previously,[12] it is, of course, true that even young people can, rarely, have thrombotic cerebrovascular lesions from no apparent cause and with a normal blood pressure. However, we do not know the true incidence of such episodes. Aring and Merritt[1] had not encountered a single patient under the age of 30 and had one under 40 years of age in their series of 106 cases of cerebral thrombosis, verified at autopsy. The Registrar General's Statistical Review of England and Wales, 1961, records that of 22,368 females who were certified to have died of cerebral embolus or thrombosis, one was between 15 and 30 years of age, two were between 30 and 35, nine were between 35 and 40, and eighteen were between 40 and 45. We do not know the morbidity incidence.

On the other hand, Oliver,[7] commenting on the incidence of coronary thrombosis in women taking oral contraceptives, reported that over a period of 12 years he had seen 144 women under 45 years of age with ischemic heart disease. Sixty-two of these women presented with acute myocardial infarction, and two were taking oral contraceptives and continued to do so.

It is perhaps pertinent that Egeberg and Owren, in a study of blood coagulability in women taking Enovid, reported an increase in Factor VIII and possibly an increase in Factor VII. Haber[5] reported a case of Factor X (Stuart Power factor) deficiency in a patient, with remissions during pregnancy, who responded well to treatment with norethynodrel.

It remains to be seen whether there is a true increase in the incidence of thrombotic lesions in women taking oral contraceptives, and whether these drugs do increase the coagulability of the blood but, obviously, these cases should be reported and the possible serious side effects, however remote, of these drugs should be borne in mind.

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The drinking driver*

Interesting clinical and sociological findings emerged from a survey of 392 drivers arrested on suspicion of being under the influence of alcohol. All were examined during my 6-year tenure of office as Divisional Police Surgeon (part time) in the City of Manchester (1958-1964). In the clinical picture which emerged, several features manifested themselves with such consistency and clarity that their importance has to be stressed.

In compliance with legal requirements all drivers were given the right of refusal to examination. Here a pattern emerged in which the more sober the driver, the more anxious he was to agree to examination. At the other extreme there was even more eagerness to clutch at the straw of refusal. Such

*Based on an article by the same title published in the British Medical Journal, December 26, 1964, by permission.

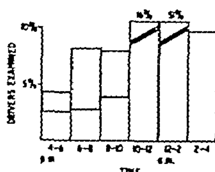


Fig. 1. Percentage of drivers examined in relation to time of examination. Shaded areas show drivers examined after pre-Christmas office and works parties. (From Freeman, S.: The Drinking Driver, *British Medical Journal*, December 26, 1964, page 1634, by permission.)

drivers were carefully observed over a period of 15 to 20 minutes, and assessment thus proved to be relatively simple. At the same time it would be preferable to copy the New York State technique by making agreement to examination a condition of holding a driving license.

Examination, after consent given in writing, proceeded generally along lines laid down in the British Medical Association publication *Recognition of Intoxication*. A careful assessment had to be made of the over-all picture, giving due credit to tests satisfactorily performed and making full allowance for fatigue and for anxiety due to arrest, always bearing in mind the axiom, "With the exception of the smell of the breath, each and every sign can be explained by a cause other than alcohol." On this premise, excluding other causes, the following appeared with significant regularity: (1) Slurred speech. (2) Impaired memory. (3) Poor coordination. (4) Full, bounding pulse. The pulse was always abnormally rapid (range of 100 to 130), but the rate was deliberately discounted since such was consistent with the natural worry and excitement of arrest. A similar interpretation was placed on the regular finding of blood pressure elevated 20 to 40 mm. Hg above the age norm. Both the rapid pulse and the raised blood pressure were regarded as of no value in the final assessment. (5) Widely dilated pupils with little or no reaction to strong light. Such was evidenced in 98.2 per cent of the cases certified on examination and was considered to be of the greatest diagnostic significance. Its importance has received insufficient emphasis in the appropriate medical literature. (6) Fine lateral nystagmus. This was noted in 96 per cent of the cases and corroborates opinion emphasized by many authorities. Its diagnostic value was considered to be second only to the state of the pupils. However, attention must be drawn to its temporary disappearance when the level of alcohol in the blood becomes exceptionally high, when the driver is patently drunk.

Two cases were seen in which the arrested driver, believed to be incapacitated by alcohol, was found to be in an advanced state of hypoglycemia. Both individuals made speedy and dramatic recovery with appropriate emergency treatment. Since the signs so closely resembled those produced by alcohol (grossly slurred speech, staggering gait, disorientation, etc.), the importance of eternal vigilance in examination is stressed.

ANALYSIS OF RESULTS

Age incidence showed the large majority of drivers (71 per cent) to be between 20 and 40 years old. Teenagers were rare (1 per cent), and in an age when denigration of youth is fashionable—and sometimes justifiable—the figures are most heartening.

Occupations were most varied, but in spite of the dangers of loss of license almost two thirds (63.5 per cent) were dependent upon driving for a livelihood. Employers are largely to blame for lack of firm discipline. All classes were included, one third being of executive or professional standing; 8 (2 per cent) were doctors. No women or members of the Jewish race were seen. It has long been established that the latter have little interest in alcohol.

Time of examination was usually after midnight when licensed premises and drinking clubs close. The notable exception was the pre-Christmas week, when many arrests occurred during the afternoon after office and works parties. This is clearly shown in Fig. 1. The major responsibility for such a state of affairs rests with well-meaning but stupid employers.

Urinalysis was of minimal value since present legislation lays down no maximum level. Juries paid scant regard to such forensic findings. A sample survey in this series showed over 75 per cent with blood/alcohol over 200 mg./100 ml.

Certification and disposal findings showed that 323 drivers (82.4 per cent) were certified, of whom 292 (90.4 per cent) were convicted.

Escape route was shown to be in frequent use. Many drivers under the influence of alcohol and involved in a crash retained sufficient cunning to pretend or exaggerate injury and insisted on removal to a hospital casualty department out of police hands. By the time the hospital investigations were completed, so was the sobering-up process. Legislation should be enacted to ensure that all drivers removed to hospital after road accidents undergo some form of chemical analysis to determine the level of alcohol, if any, in the blood stream.

Conclusions. Much rethinking is urgently required to deal with the menace of the drinking driver—and the medical profession should lend all assistance. Our laws are outdated and totally inadequate to combat the ever-growing problem. The tragedy is that the magnitude of the dangers is still not appreciated by the public at large. Propaganda must be intensified—via press, radio, and television, and above all, by the good example of leaders in all branches of the community.

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The hexosamine:collagen ratio as a measure of biochemical age in Hiroshima atomic bomb survivors[1]

Exposure of laboratory animals to sublethal amounts of whole body irradiation results in shortened life span in excess of that attributable to the known carcinogenic effect of radiation.[1-4] Such animals are said to exhibit accelerated aging (defined as the premature appearance of a variety of degenerative changes commonly associated with senility). This report explores the relationship between aging and exposure to ionizing radiation in survivors of the atomic explosion in Hiroshima, Japan. The parameter of aging selected for this study was the ratio of mucopolysaccharide ground substance, including hexosamine, to collagen; this age marker has been shown to be age-dependent in rats, guinea pigs, rabbits, and man and has been generally accepted as a measure of biochemical age.[4-6] The ratio decreases with advancing age.

Determinations in the present study were performed on samples of skin and aorta obtained from men autopsied at the Atomic Bomb Casualty Commission during the period 1962-1964. Tissues were stored at −20°C. until tested. Cases were grouped by age without knowledge of the clinical or autopsy findings, as follows: tissue from a proximally exposed individual (less than 1,400 meters from the hypocenter at the time of the explosion) was paired with tissue from an individual not in Hiroshima at the time of the bomb. Only tissue from proximally exposed survivors was employed because there is some doubt as to the biologic significance of the amounts of radiation absorbed at distances much in excess of 1,400 meters. The determinations were performed on each experimental pair at the same time and all tests were done in duplicate.

Chemical determinations were performed on dried, defatted, acid-hydrolyzed skin and aorta in the following fashion. The hexosamine content was determined by Bitz modification[7] of the Elson and Morgan method after absorption and elution from Amberlite IRC 50 resin.[8] The hydroxyproline content was determined by the Neuman and Logan method[9] as modified by Martin and Axelrod.[10] With each experimental pair the results were expressed separately for skin and aorta as the ratio of hexosamine to collagen. The calculation of collagen content was based upon the knowledge that this substance contains 13.2 per cent hydroxyproline.

Hydroxyproline:collagen ratios were determined in samples of skin and aorta obtained from 14 experimental pairs (28 individuals). In 11 of the pairs, the hexosamine:collagen ratio of the skin was smaller in the exposed member than in the nonexposed one. By the use of combinatorial analysis, it can be shown that the probability of obtaining such a distribution by chance sampling is statistically unlikely ($p < 0.05$). In determinations performed on aorta, the exposed members of the same 11 pairs also showed lower ratios.

Demonstration of these biochemical alterations in persons with no other known morphologic, clinical, or chemical indication of previous exposure to significant amounts of ionizing radiation suggests the possibility of accelerated aging among proximally exposed survivors of the atomic bomb. Such a postulation, however, is directly dependent upon the validity of the hypothesis that the hexosamine: collagen ratio is a specific age-dependent measurement. Although there can be little doubt that the ratio varies directly with age, the specificity of this parameter has not been unequivocally established. The problem of specificity is, of course, complicated by the large number of hypotheses concerning the etiology and pathogenesis of aging. A proposed parameter which appears to be specific and to fit comfortably into one theory of aging may be completely incompatible with another hypothesis. None of the currently popular concepts adequately explains the protean manifestations of aging. Although this inadequacy has been cited as evidence that more than one process is in operation, it appears to be equally plausible that studies on aging, which, to date, have largely been descriptive, have not defined the primary alteration; the possibility certainly exists that the manifold expressions of senescence merely reflect the fundamental character of the biochemical or immunological abnormality.

The foregoing discussion directly relates to the use of the hexosamine:collagen ratio as a parameter of aging. Although on the basis of current concepts the described alterations in hexosamine and/or collagen strongly suggest the presence of accelerated aging among proximally exposed survivors of the atomic bomb in Hiroshima, this association should be considered to be tentative and should be reconsidered as new information becomes available concerning spontaneous and experimentally induced aging.

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Letter to the Editor

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April 21, 1965

To the Editor:

In a prior communication (*American Heart Journal* 69:229-232, February, 1965) we described a technique of lymphatic cannulation that is inexpensive, dependable, and simple to perform. The article included a photograph showing a lymphatic cannulation set which was intended to serve as a model for others interested in making their own. In the interest of brevity, a detailed discussion of the methodology of cannula preparation was omitted. However, after publication of the article, several persons indicated that they experienced difficulty in making tapered polyethylene cannulae. Since the photograph and brief description of the lymphatic cannulation set apparently did not provide readers with a sufficiently clear understanding of how lymphatic cannulae are fashioned, several points which have been most helpful in simplifying this task in our laboratory are detailed below.

Lymphatic cannulae are prepared by stretching heat-softened polyethylene tubing (PE 90) around small intraluminal wires. The objective of the procedure is to reduce the external diameter of the tubing without disrupting the continuity of its lumen. The intraluminal wire maintains patency during heating, prevents curling of the cannula tip during cooling, and subsequently may be used as a stylette during lymphatic cannulation. The cross-sectional area of the tapered portion of a particular lymphatic cannula depends on the diameter of the intraluminal wire used in its preparation. Small wire suitable for this purpose is readily available in the usual hospital area, e.g., spinal needle stylettes or small pipette cleaning wires. The wire should be slightly larger than the segment of polyethylene being prepared, so that it can be easily removed from the finished cannula.

A small, localized source of heat with relatively constant temperature is most desirable. An alcohol lamp is superior to a Bunsen burner in this regard. Recently we have found the most dependable source of heat to be an ordinary electric soldering iron, preferably not the soldering gun varieties. The temperature of the iron should be permitted to stabilize prior to its use in preparing lymphatic cannulae.

A wire, approximately 5 inches long, is inserted into the lumen of a segment of polyethylene tubing approximately 4 inches long and is positioned so that it extends beyond the tube at both ends. The ends of the tube are held between the thumb and forefinger of each hand, and an area about 1 inch from one end of the tube is brought into close proximity with the heated soldering iron. At the optimal distance from the source of heat polyethylene softens, but does not melt or burn. This effect is circumferentially uniform if the tube is slowly rotated through 180-degree arcs, in alternating directions. Softening begins almost immediately and the material becomes semisolid in less than 1 minute. The cannula is formed by pulling gently on one end of the tube while the other is held immobilized. It is important that this step be one of "stretching" rather than "jerking," and that all motion be stopped before the tubing breaks or perforates. It is immediately withdrawn to a point 2 or 3 inches from the soldering iron and allowed to cool for a few seconds before proceeding further. Polyethylene solidifies almost instantly when removed from the source of heat.

If heating is prolonged and melting occurs, polyethylene tends to form a knob-like protrusion on the dependent side of the tubing. However, redistribution of the accumulated material, and successful completion of the cannula preparation, may still be possible. In this instance the tubing is again held over the source of heat, but in a position that brings the irregularity in the polyethylene nearly into contact with the iron. It is held motionless in this position until the area has remelted, after which the tubing is slowly rotated 180 degrees and gently drawn out, while being slowly retracted from the source of heat.

The length of the tapered portion of the cannula is extended by sequential heating, stretching, and cooling of areas immediately adjacent to those which have already been completed. The intraluminal wire is removed after the lymphatic cannula has been stretched and shaped into the desired form. In most instances this is simply accomplished by holding the cannula in one hand while the wire is gently rotated and pulled out of the lumen with the other. Occasionally, in the making of cannulae with tips longer than 10 mm., the polyethylene may become securely attached to the intraluminal wire. Even then a perfectly formed cannula may be salvaged. All excess polyethylene adhering to the wire beyond the tip of the cannula is shaved off with a razor or scalpel blade. Then, while the wire is being held by the exposed area in a hemostat or small needle holder, the cannula is gently rotated until loosened and then slid off the end of the wire. The tip of the cannula is cut off squarely at the desired diameter and the completed cannula is shortened to fit its stylette by cutting off excess tubing.

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THE DOCTOR HAS A HEART ATTACK. By Samuel Goodstone, M.D. Boston 1964 Beacon Press, 118 pages. Price $3.50

Written primarily for the layman this is a highly readable and informative account of the experiences of a physician who had had a myocardial infarction. Skillfully woven into the bold narration are brief digressions into various aspects of cardiac diagnosis and therapy including cardiac nursing anticoagulants, the cardiac chair and the use of electrocardiography and serum enzymes. This is followed by sections on the pathogenetic aspect of coronary artery disease and on the problems of readjustment and rehabilitation faced by patients convalescing from myocardial infarction. The book concludes with a set of questions and answers on topics related to coronary artery disease. A short glossary is appended at the end and will help considerably with the medical terminology employed throughout the book. This contribution is highly recommended to physicians and patients interested in coronary artery disease.

BLOOD PROGRAM IN WORLD WAR II. Edited by Colonel John B. Coates, Jr. MC USA, and Elizabeth M. M. Fetridge, M.A., Washington D.C., 1964 Surgeon General, Department of the Army (Superintendent of Documents Government Printing Office), 922 pages. Price $8.

This volume is another in the series in which the official history of the Medical Department of the United States Army in World War II is recorded. These volumes have been prepared by the Historical Unit, United States Army Medical Service, and published under the direction of the Surgeon General of the United States Army. This volume records the development of the very extensive blood program and all of its many aspects before during and after World War II with an additional section concerned with the similar problems in the Korean War. The organization and presentation are good and lucid. Some aspects of the many problems encountered are presented in considerable detail, which is essential if it is to serve the useful function as a historical guide. It is doubtful that there are very many people who are aware of or have given consideration to the tremendous logistical and practical problems concerned with the procuring of large quantities of whole blood and blood products and the supplying of these to areas far removed from the site of collection and processing. An analysis of some of the problems encountered in light of the policies and procedures current at that time are examined and presented in a forthright manner. Errors judgment, delays in implementation, and other critical comments are presented in a constructive manner.

The magnitude of the problem of supplying such a perishable product as fresh whole blood, which must be processed with such infinite attention to detail, is almost overpowering. A review of this book is a humbling experience. The admirable manner in which these problems were solved is a tribute to all those concerned and an accomplishment of which our entire nation should not only be aware but for which it should be eternally grateful. I believe that this historical record will serve the purpose quite well as outlined by the authors. Without hesitation I recommend this book to all physicians as well individuals engaged in paramedical pursuits.

SUDDEN CARDIAC DEATH. Edited by Borys Surawicz, M.D. and E. D. Pellegrino, M.D., New York 1964 Grune & Stratton, Inc. 222 pages. Price $9.50

This book represents a symposium held at the University of Kentucky on Oct. 4-5 1963. Included are discussion of anatomic factors concerned with sudden death mechanisms, the vulnerable electric phase ventricular fibrillation ventricular asystole coronary occlusion, pulmonary embolism and prevention. The material presented varies in quality. For example the illustrations on pages 72 and 73 are poor. Most of the material presented should be well known to most internists and certainly to cardiologists, but some physicians and undergraduate students may find the book worth reading. As in the case of most symposia the subject can receive only superficial consideration.

CLINICAL ELECTROCARDIOGRAMS. Edited by Stephen R. Elek, M.D. F.C.C.P., F.A.C.P., Associate Clinical Professor of Medicine University of Southern California. Springfield, Ill., 1965 Charles C Thomas, Publisher 236 pages. Price $11.75

This book has 58 contributors. Thus, it is not surprising that some chapters are only a page or two long, inadequately illustrated and the entities inadequately discussed. The section entitled "Congenital Heart Disease and Vectorcardiography" consists of one-half page of text on tetralogy of Fallot in an 8-month-old infant and presents an unbelievably unsatisfactory description of the electrocardiogram of tetralogy of Fallot. *In fact* the electrocardiogram is certainly not typical of the severe type, and the superior plane projection of the vectorcardiogram for the tetrahedron is referred to as the horizontal plane. Again on page 160 the case of

a patient with cor pulmonale and $S_1S_2S_3$ syndrome in the electrocardiogram is discussed in such a manner that the reader may gain the impression that an $S_1S_2S_3$ pattern is found only in patients with cor pulmonale. This is certainly not true.

This book is a collection of discussions of patients with various diseases, some cases documented by autopsy and some poorly illustrated (page 21). This book will be of little value to anyone.

AN OUTLINE OF PULMONARY FUNCTION AND PULMONARY EMPHYSEMA. By Eugene Rosenman, M.D., Assistant Clinical Professor of Medicine, Loma Linda University School of Medicine, Los Angeles, Calif. Springfield, Ill., 1964, Charles C Thomas, Publisher. 137 pages. Price $6.50.

This brief volume is of value as an introduction for clinicians and students to a complicated field of investigation which has produced a literature that is often difficult. The chief faults of the book lie in its failure to adequately cover important divisions of pulmonary function, such as pulmonary diffusion and surface tension, and its sparing use of illustrative figures. Current clinical and physiologic distinctions which have been drawn between uncomplicated chronic bronchitis and pulmonary emphysema are not presented. Recent developments in the pathologic and radiologic study of these diseases are not included. Although the bibliography lists 201 references, numerous important articles are not cited.

LA ENFERMEDAD DE CHAGAS CONGENITA. By Jorge E. Howard, Profesor Extraordinario de Pediatría, Facultad de Medicina, Universidad de Chile. Santiago, 196–, 92 pages.

This monograph summarizes our knowledge of one of the more unusual aspects of Chagas' disease: that of the infection acquired in utero. Many interesting facts emerge from this book: some of the mothers of infants with congenital Chagas' disease are unaware of their own infection; the onset of symptoms is variable, ranging from 1 to 90 days after birth; hepatosplenomegaly, cutaneous lesions, and neurological manifestations lead to the diagnosis. The differential diagnosis includes congenital syphilis, toxoplasmosis, and the hemolytic anemias of the newborn. The diagnosis is established by serology and by demonstration of the parasitemia. The therapy is unsatisfactory and the mortality is high. Clinical evidence of cardiovascular disease was found in only 1 of the 15 patients studied by the author and in 1 of the additional 16 patients reported in the literature; however, microscopic study revealed cardiac lesions in 7 of 10 autopsied cases. The low incidence of clinical cardiovascular complication reported in this series is apparently similar to that reported in adult patients with Chagas' disease seen in Chile.

A SYNOPSIS OF CARDIOLOGY. By D. Weitzman, M.D., M.R.C.P., Cardiologist, St. Bartholomew's Hospital, London, with J. M. H. Campbell, O.B.E., M.A., M.D., F.R.C.P. Bristol, 1964, John Wright and Sons, Ltd., and Baltimore, 1964, Williams & Wilkins Co. 200 pages. Price $7.

A remarkable amount of information is contained within the pages of this Synopsis. Emphasis is placed on physical diagnosis, and the descriptions of signs and symptoms of cardiovascular disease are particularly excellent. The sections on electrocardiography, vectorcardiography, cardiac catheterization, and angiography are rather brief but the material presented has been wisely chosen. Some of the sections on therapy, i.e., the recommendations for digitalization and for the management of arrhythmias, are oversimplified and of limited usefulness. There is no information on the D.C. defibrillator and relatively little on the problems of digitalis toxicity. Surprisingly no mention is made of the use of the long-acting penicillin preparations, which many would surely prefer for the prophylaxis of rheumatic fever.

AN ELECTRON MICROSCOPE STUDY OF THE EARLY DEVELOPMENT OF THE RAT METANEPHRIC NEPHRON. Pentti Jokelainen, University of Helsinki, Finland. Acta Anatomica, Supplement 47. Basel, 1963, S. Karger (U. S. agent, Albert J. Phiebig, White Plains, N. Y.). 71 pages. Price $6.

This monograph describes the early development of the metanephron unit of the rat as observed by modern cytological methods, including the use of reconstruction techniques based on serial sections studied by phase-contrast and electron microscopy. The course of development is traced from the primitive metanephrogenic blastemal cap to the stages characterized by the initiation of glomerulogenesis. The subject matter is clearly and concisely presented with the help of excellent diagrams. The reproduction of the electron micrographs is of high quality throughout.

LEITFADEN UND ATLAS DER ANGIOLOGISCHEN DIAGNOSTIK. By Dr. Med. Arnold Kappert, Bern and Stuttgart, 1964, Hans Huber. 184 pages.

This atlas on the diagnosis of arterial disease is well illustrated with excellent photographs of lesions, diagrams of apparatus, anatomic and functional principles and angiograms. The author, of course, emphasizes the approach and procedures used in West Germany for the study of the arterial, venous, capillary, and lymphatic vessels. For example, in a study of adequacy of the peripheral circulation, emphasis is on the use of oscillography rather than plethysmography or thermography. Nevertheless, the reader has an opportunity to learn the value of oscillography in diagnosis by studying the monograph. This is a good atlas and should be useful to students and physicians.

Accion de las Catecolaminas en el Sistema Nervioso Central. By Dr. Carlos Muñoz, Profesor Titular de Farmacologia, Facultad de Odontologia, and Profesor Extraordinario de Farmacologia, Facultad de Medicina, Universidad de Chile. Santiago, 1963, 200 pages.

This monograph presents a carefully written review of the literature on the physiologic and pharmacologic effects of catecholamines in the central nervous system. The biosynthesis, storage, liberation, inactivation, and excretion of catecholamines are discussed in detail in the initial chapters. Subsequent sections are concerned with the effect of catecholamines on the brain and spinal cord, on the cerebral circulation, and on neuroendocrine functions. This material is presented in a clear, elegant style and is documented with an extensive bibliography.

Announcements

Postgraduate Course on Medical Hypnosis. A postgraduate course on medical hypnosis is being offered to physicians and dentists by the Division of Graduate Medicine, University of Pennsylvania. The Department of Psychiatry is in charge of organizing the sessions.

There will be 20 weekly afternoon sessions for a total of 80 hours beginning Sept. 29, 1965.

It is, at the present time, one of the few courses offered which meets with the recommendations made by the American Medical Association Committee on Hypnosis.

During the first part of the course basic concepts of hypnosis will be taught through lectures on psychiatry and hypnosis, demonstrations, and supervised practical work in hypnosis.

The latter part of the course will cover clinical applications of hypnosis. Here there will be sessions limited to psychiatrists and other sessions limited to general practitioners, dentists, and specialists other than psychiatrists.

The course will be given at the Institute of the Pennsylvania Hospital, 111 North 49th Street, Philadelphia, Pa., 19139.

The teaching staff of twelve is headed by Lauren H. Smith, M.D., Professor and Chairman of Psychiatry, Department of Psychiatry, Division of Graduate Medicine, University of Pennsylvania. Dr. Smith is Consultant for Medical Development at the Institute of Pennsylvania Hospital.

An International Conference on Diabetes in the Tropics will be held in Bombay, India, from J[illegible] 20 to 22, 1966. The deliberations of the Conference will be in English.

The following aspects of tropical diabetes will be discussed: (1) incidence of diabetes, its mortality and morbidity in the tropics; (2) diabetes in the young; (3) pancreatic diabetes; (4) diet, with particular reference to high carbohydrate content in diabetes in the tropics; (5) complications of diabetes and their prevention; (6) management of diabetes in the tropics; (7) prevention of diabetes.

The Conference is open to all the workers in the field of diabetes irrespective of whether they are members of the Diabetic Association of India provided that their paper is accepted by the Organizing Committee.

Abstracts of papers along with the title of the article and the names of all the authors should reach the Organizing Secretary by Oct. 15, 1965, and the full text of the article along with the list of references by J[illegible] 1, 1966. Arrangement can be made to project 35-mm slides and 16-mm films if prior intimation is given when the paper is submitted. Time allotted to each paper including that for films and slides, shall not exceed 10 minutes.

For further information, write to the Organizing Secretary, World Congress on Diabetes in the Tropics, Diabetic Association of India, Maneckji Wadia Bldg., Mahatma Gandhi Road, Bombay 1, India.

A Course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital and Medical Center by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M. Dec. 6 through 11, 1965. Registration is limited to 30.

Further information and copy of the lecture schedule may be obtained from the Secretary, Cardiovascular Institute, Michael Reese Hospital and Medical Center, 29th St. and Ellis Ave., Chicago 16, Ill.

A Symposium on Macromolecular Metabolism, the seventh international basic science symposium of the New York Heart Association, will be held in New York City at the Biltmore Hotel, Friday and Saturday, Dec. 3 and 4, 1965.

For information on registration, write to the Symposium Committee, New York Heart Association, 10 Columbus Circle, New York, N. Y. 10019.

Applied Office Psychiatry. A postgraduate course in office psychiatry is being offered to physicians by the Institute of the Pennsylvania Hospital, 111 North 49th Street, Philadelphia, Pa., 19139.

The course is designed to give the maximum of know[illegible] useful information to the practicing physician who is interested in improving his ability to manage the psychiatric problems commonly encountered in the *practice of medicine. In keeping* with this emphasis on practical usable information, theoretical material will be kept to a minimum. The course will consist of twelve 4-hour weekly sessions beginning Sept. 29, 1965.

A unique approach to the presentation of clinical material has been developed to make these problems [illegible] and meaningful to the nonpsychiatrist. At each session, the student will observe through a one-way mirror a patient being interviewed by an experienced psychiatrist. Patients will have problems commonly encountered in general medical practice. Lectures and round table discussions will also be used.

The faculty will include some of the outstanding *teachers of psychiatry in the Philadelphia area. Each* of the lectures and following interviews will be handled by a different faculty member permitting the student to see a variety of approaches to the patient. To preserve continuity the discussion of the interviews and the subsequent group seminars will be led by a single instructor.

The topics to be covered are: *Session One*: The Doctor-Patient Relationship; *Session Two*: The Anxious Patient; *Session Three*: The Depressed Patient; *Session Four*: The Multiple Complainer; *Session Five*: The Impulsive Patient; *Session Six*: Marital Problem; *Session Seven*: Frigidity, Impotence and Other Sexual Disturbances; *Session Eight*: Overeating and Oversmoking; *Session Nine*: Alcoholism; *Session Ten*: Psychosomatic Disease; *Session Eleven*: Psychosomatic Disease; *Session Twelve*: Psychiatric Emergencies.

Cardiovascular Pulmonary Emergencies. The Division of Continuing Education of The University of Texas Graduate School of Biomedical Sciences at Houston and the Frederick R. Lummis Medical Foundation will present a one-day symposium entitled "Practical Aspects of Cardiovascular Pulmonary Emergencies" on Saturday, Oct. 9, 1965, in the Texas Medical Center in Houston. This course is intended to give practicing physicians a useful and authoritative review of current medical and surgical approaches used in managing cardiovascular pulmonary emergencies in adults. The participating guest speakers will be: C. Walton Lillehei, M.D., Professor of Surgery, University of Minnesota, Minneapolis, Minn.; Myron Prinzmetal, M.D., Chief, Department of Cardiology, Cedars of Lebanon-Mount Sinai Hospitals of the Los Angeles Jewish Medical Center; and Herbert Otto Sieker, M.D., Professor of Medicine, Duke University School of Medicine, Durham, N. C.

For additional information write to: Division of Continuing Education, The University of Texas Graduate School of Biomedical Sciences at Houston, 102 Jesse Jones Library Bldg., Texas Medical Center, Houston, Tex., 77025.

Potassium and the Heart, a 2-day symposium will be held at the hospital auditorium of the University of Kentucky Medical Center in Lexington, Kentucky, on Oct. 1 and 2, 1965.

For any additional information contact Dr. Borys Surawicz, Department of Medicine, University of Kentucky College of Medicine, Lexington, Ky.

The American Heart Journal has recently published a number of succinct articles devoted to a survey of diuretic therapy. This series has appropriately appeared in the section "Appraisal and Reappraisal of Cardiac Therapy" and was prepared by Dr. Arthur C. DeGraff and Dr. Alan F. Lyon. The articles have been widely popular and the demand for reprints has far exceeded expectations.

The Editors have arranged with the publisher of the American Heart Journal to make available a complete paperback reprint of all articles. The booklet may now be purchased immediately direct from the publisher or through medical book stores, at a cost of $3.50 per copy.

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Editorial

Tension, drugs, and premature systoles

*Leonard S. Dreifus, M.D.**
Yoshio Watanabe, M.D.
Philadelphia, Pa.

Disturbances in cardiac rate and rhythm have concerned patients and physicians from the beginning of medical writings. Even today, with precise methods of identification and potent antiarrhythmic agents, the association of ectopic mechanisms with ventricular fibrillation and cardiac standstill carries a potentially ominous feeling. Furthermore, the sinister correlation of serious cardiac disease and premature systoles cannot be denied. Although the actual incidence of ectopic impulse formation is unknown, electrocardiographic monitoring in health and disease has brought into sharp focus the prevalence of premature systoles.[1] Analysis of 66,707 records in the Heart Station of Hahnemann Medical College revealed 3,359 instances of premature systoles; associated myocardial disease was present in 2,504 cases, or 75 per cent. Although this is a preselected hospital population with random electrocardiograms, it may imply that persistent ectopic beating appears more often in the presence of organic heart disease than in its absence. On the other hand, multifocal or paired premature systoles are invariably associated with an underlying cardiac disorder.[2] It has been noted that various extracardiac factors also modify the incidence of cardiac arrhythmias. Among these, the association of premature systoles with anxiety states, dissipation, and certain common drugs merits discussion. However, because of the frequency and benignity of these arrhythmias, their actual incidence is virtually undocumented in the medical literature.

Tension

For centuries it has been recognized that the heart is particularly susceptible to emotional stimuli, and one of the earliest observations of emotionally induced tachycardia was made by Avicenna in the tenth century.[3]

Although palpitations are commonly attributed to increased awareness of the heart or to sensations produced by sinus tachycardia or increased stroke volume, careful observation of these patients may reveal a high incidence of cardiac arrhythmias at the time of the palpitations. Psychogenic factors may precipitate ectopic rhythms in normal hearts as well as in those with structural disease. Although similar

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factors are operative in both groups, patients with cardiac abnormalities are more vulnerable to their development. Arrhythmias associated with psychosomatic disorders result from the interaction of many factors. Stimuli from the central nervous system affect both the sympathetic and parasympathetic systems and the endocrine glands (especially the thyroid and adrenal). The important central nervous system centers involved are the cerebral cortex, hypothalamus, pituitary, and medulla. This inference is substantiated by the observation that the injection of epinephrine and the increased release of epinephrine and norepinephrine in patients with anxiety reactions have similar effects on the heart. These factors acting alone or in combination may result in the formation of ectopic impulses.

Premature systoles have been known to occur as part of the reactions to pain, elation, fear, resentment, humiliation, excessive hostility, compulsiveness, anger, depression, and excessive fatigue.[4] Although the chronic stress of the individual's life situation is considered to be the underlying etiological factor, an acute exacerbation may precipitate an added degree of tension with the resultant production of arrhythmias. Most physicians agree that there is rarely a healthy individual who has never exhibited premature systoles. They come and go without detectable reason and are of no prognostic significance. In normal hearts, sudden death due to emotional strain is rare although Katz[4] observed paroxysmal ventricular fibrillation in an individual whenever an electrocardiograph machine was wheeled into the room. Nevertheless, the presence of cardiovascular disease with its many manifestations and its known tendency to cause sudden death has a profound effect on the patient's mental state. Furthermore, disorders of rhythm resulting from emotional disturbances or myocardial dysfunction may in turn result in mental symptoms which further aggravate this condition.

Since premature systoles may be an early sign of myocardial disease, a complete examination is indicated. Only prolonged observation is necessary to reveal the onset of cardiac disease which otherwise would have escaped detection. The physician should possess the necessary information and prestige to explain these disturbances in rhythm to the patient, and every effort should be made to lead a normal life. It may even be suggested that during the examination the physician should not listen too long to a particular region of the chest or relate significant findings to the patient.

Appropriate therapy should include manipulation of the life situation and efforts to help the patient deal more constructively with his problems and conflicts. Nothing will convince the patient so readily of the innocence of his arrhythmia as the lack of restrictions. Observation and registration of the pulse or rhythm should be discouraged. In some instances, premature systoles may engender an unpleasant impact or blow on the chest or produce an uncomfortable intermittence of the pulse, so that pharmacologic therapy may be required. Small doses of phenobarbital or an appropriate tranquilizer may reduce the awareness of the ectopic beats. Rarely is one required to exhibit an antiarrhythmic agent for the treatment of premature systoles due to anxiety. When this is necessary, quinidine sulfate (0.4 Gm.) administered four times daily will depress ectopic supraventricular or ventricular beats in a majority of patients. Alternative choices include procaine amide (500 mg.) or diphenylhydantoin (100 mg.) four times daily.

Nicotine

The effects of nicotine are complex because of multiple sites of action. The rate of the heart is usually slowed at first due especially to stimulation of the central vagal nuclei and cardiac vagal ganglia. Later or after large doses, tachycardia is prominent because of the stimulation of cardiac sympathetic ganglia. An increased discharge of epinephrine from the adrenal medulla and the urinary excretion of catecholamines are present after heavy cigarette smoking. In most persons smoking 1 or 2 cigarettes causes an increase in the heart rate of 15 to 25 beats per minute, a rise in blood pressure of 10 to 20 mm. Hg, and a slight increase in cardiac output. A decrease in coronary flow or constriction of the coronary arteries as visualized by selective coronary angiography is incon-

sistent and cannot be directly indicted as a cause of premature systoles in the normal or abnormal heart.[6]

Although the precise incidence of premature systoles due to smoking is unknown the association has been known for many years and was discussed even at the time when one spoke only of an intermittent pulse. Several interesting case reports of smoking and ectopic rhythms have appeared in the literature,[7,8] and can be reviewed for more detailed information. It appears that coronary artery disease may render the heart more vulnerable to ectopic beating due to nicotine. In those instances, the use of digitalis or its glycosides may be required to control atrial premature systoles or tachycardia in addition to the cessation of smoking.

Coffee

All parts of the circulatory system are affected in some way by coffee. Caffeine is known to stimulate the myocardium directly and experimental studies have demonstrated an increase in the amplitude of excursion rate, and cardiac output. Eventually this stimulation may be great enough to engender cardiac irregularities. In most instances, ectopic impulse formation regresses slowly with suppression of the coffee habit.[9]

Alcohol

The cardiac effects of alcohol are slight and inconsistent. The widespread belief that the coronary arteries are dilated and coronary flow increased in normal hearts or in the presence of coronary heart disease by moderate doses of alcohol is unsupported by acceptable clinical evidence. Likewise, the association of intemperance and premature systoles is without precise documentation and probably overrated. Except for a reorientation of personal habits and environment no specific therapy appears to be appropriate.

Amphetamine

Many "reducing pills" contain varying amounts of amphetamine or thyroid hormone and may be responsible for the initiation of premature systoles or ectopic rhythms. Frequently patients may conceal the fact that they are taking appetite suppressants and the etiology of the ectopic beats may remain obscure unless the physician can elicit an adequate history. Moderate doses of amphetamine (30 to 40 mg.) produce a rise in systolic and diastolic pressures as well as an increase in cardiac output and work. A direct myocardial action may precipitate ectopic beating in normal persons as well as in patients with heart disease.[1] Although supraventricular tachycardia appears most frequently circulatory collapse, high-grade A-V heart block and premature systoles have been reported after large doses of amphetamine. Withdrawal of this agent is mandatory when side effects appear.

Thyroid drugs

The thyroid hormone may affect the heart in several ways: increase blood volume and cardiac work, heighten the sensitivity to catecholamines, stimulate the sympathicoadrenal system, and instigate disturbances in the pituitary diencephalon and hypothalamus. Direct or indirect stimulation of these systems may initiate the formation of ectopic impulses. Thyroid hormone increases the basal metabolism in the atria more markedly than in the ventricles,[12] and may explain the pathophysiologic basis for the atrial arrhythmias so characteristic of hyperthyroid heart disease. Most authors agree that underlying cardiac disease predisposes to arrhythmias associated with hyperthyroidism. Hence the return to the euthyroid state by withdrawal of the offending agent may be insufficient to control the ectopic mechanism. Digitalis or its glycosides should be administered in the presence of multiple premature atrial systoles, atrial tachycardia, flutter or fibrillation. Likewise the use of procaine amide or lidocaine may be necessary to control ventricular ectopic beating.

Finally it should be emphasized that any approach to the identification and treatment of cardiac arrhythmias is predicated on a precise diagnosis of the abnormal rhythm as well as the reversion of the pathophysiologic processes contributing to the initiation of the abnormal mechanism. In this regard, extensive and well-controlled statistical studies utilizing electrocardiographic monitoring to determine the inci-

dence of cardiac arrhythmias in health and disease may be desirable. So far one finds that very little can be added to the classic observations of MacKenzie. It may be stated that when the extrasystole is the only abnormal sign the prognosis is a favourable one and where it is associated with other signs the prognosis is to be based upon these other signs.[13]

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Clinical communications

Quantitative criteria for the diagnosis of dorsal infarction using the Frank vectorcardiogram

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The qualitative characteristics of QRS loops in dorsal infarction are increased magnitude and duration of the anterior forces resulting from loss of posterior electrical potentials.[1-4] When such alterations are great in the distal half of the QRS loop reversal of rotation may occur in the horizontal or sagittal planes,[6] making the diagnosis relatively easy—if right ventricular enlargement need not be considered. In the majority of cases, however, normal rotation is maintained in the reference planes reflecting anterior-posterior (Z axis) forces, and the diagnosis is therefore considerably more difficult.

Quantitative criteria are needed which will identify QRS loops resulting from dorsal infarction but maintaining normal rotation. Such criteria must acknowledge the presence of a normal variant[7] which occurs in about 15 per cent of all age groups and in which the anterior forces are prominent. The criteria must effectively separate such normal QRS loops from those resulting from dorsal infarction.

In this study a set of 4 criteria will be offered based on statistical comparison of normal and infarct groups, which in combination, appear to meet the requirements for effectiveness.[8]

Materials and methods

Patients were admitted to the study only if serially increasing R and T waves were noted in ECG Leads V_1 or V_2 during an illness diagnosed clinically as acute myocardial infarction.[9] ECG evidence for associated anterior or inferior infarction did not disqualify patients but became a basis for classification. Twenty three patients in all were admitted to the study. Of these, 16 presented normal rotation in the sagittal and horizontal planes, and thus were the vehicle for statistical study and comparison with normal subjects. Four patients with concomitant inferior infarction displayed reversal of the QRS loop in the sagittal plane (Type F infarction), whereas the other 3 were examples of combined anterior and posterior disease with horizontal or sagittal reversal.

Frank system[11] vectorcardiograms were

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visualized using a Sanborn vector system and photographed with a Polaroid camera Time dashes were generally set at 2.5 msec and occasionally at 10 msec Accurate measurement of Z axis phenomena was accomplished both by high amplification of the loops and by recording the scalar Z lead at 100 mm per second while retaining the time dashes This latter technique was first proposed by Pipberger[17]

The direction of horizontal plane 20 30 and 40 msec maximum QRS and half-area vectors were determined as described previously The total duration and maximum voltage of the anterior forces were measured from the QRS loops and from the high-fidelity Z lead Maximum posterior voltage was also measured and the anterior-posterior voltage ratio was obtained

The accession time of the anterior forces was measured from QRS onset to the peak anterior voltage This was best displayed in the amplified Z-lead The direction of the horizontal vector formed at peak anterior voltage was determined in the usual way

Similar studies were performed on 70 subjects, 18 to 73 years old who were considered to be normal on the basis of physical examination blood pressure chest x-ray film and electrocardiogram (Table I)

Table I Age groups of 70 normal subjects studied with the Frank ECG system

Age group	Number in each group
18-29	13
30-39	18
40-49	21
51-59	9
60-73	9

Fig 1 illustrates in diagrammatic fashion the horizontal loop in dorsal infarction with normal rotation as compared with a normal loop Fig 2 illustrates the high fidelity Z-lead in the same two situations. The various measurements made in this study are indicated

Results

Table II indicates the observed means and standard deviations for the several measurements described above In addition the means and standard deviations of the same measurements in 70 normal subjects are given

Data are presented for two infarct

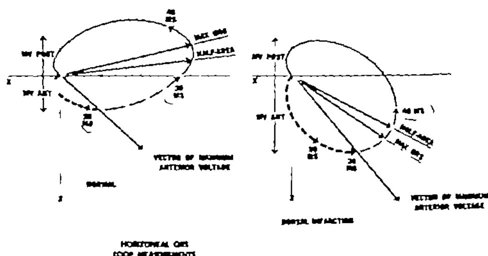


Fig 1 Horizontal plane QRS loop in a normal subject compared with that in a patient with dorsal infarction MV ANT Maximum anterior voltage. MV POST Maximum posterior voltage The bold-faced time dashes indicate the accession time of the maximum anterior forces.

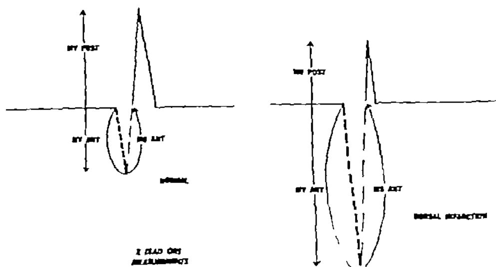


Fig. 2. High-fidelity Z axis lead in a normal subject compared with that in patient with dorsal infarction. *MV ANT*, Maximum anterior voltage. *MV POST*, Maximum posterior voltage. *MS ANT*, Total anterior QRS duration. The bold-faced time dashes indicate the accession time of the maximum anterior forces.

groups, both displaying normal QRS loop rotation in sagittal and horizontal planes. The first group of 6 patients were presumed to have pure dorsal infarction (Fig. 3). The second group of 10 patients had dorsal infarction combined with inferior infarction (Fig. 4). Data are also given for both groups combined totaling 16 patients.

Student's "t" test was used to compare the results in these three groupings with corresponding data in 70 normal subjects. Table I gives the "t" value for each comparison and its significance stated as the probability of chance occurrence.

Discussion

A glance at Table II indicates that of the eleven parameters measured eight were significant beyond the 1 per cent level for pure dorsal infarctions and for dorsal infarction combined with inferior infarction as well as for these two groups combined. It is among these significant parameters that a search was made for specific values which would serve as diagnostic criteria.

Table III displays the overlaps between 70 normal subjects and the 16 patients who were presumed to have dorsal infarcts for the eight characteristics of the anterior QRS forces which resulted in significant "t" tests. For each measurement, the point of best separation is indicated by a heavy horizontal bar. The percentages of patients falling on either side are indicated. For example, in the case of "Milliseconds anterior," it is seen that a value of 42 msec. separates 94 per cent of the infarct cases from 89 per cent of the normal cases. Stated conversely, 11 per cent false-positive and 6 per cent false-negative diagnoses resulted from the use of the 42 msec. anterior duration as a criterion when applied to the populations studied.

None of the eight significant parameters provided a satisfactory criterion. Although perfect separation of normal and diseased groups remains the ideal, it is unlikely that this can be achieved when obvious overlap occurs between normal subjects and patients. A further problem is the lack of certainty in the designation "normal," especially in the older age groups. Inevitably, a few patients who have sustained silent dorsal infarction will be included in the normal group. A further difficulty is the normal variant in which prominent anterior forces characterize the vectorcardiogram.

For these reasons, criteria were sought which would exclude 95 per cent of the normal subjects studied. When specific

Table II Statistical comparison of data in 70 normal subjects with data in 16 patients presumed

Measurement	70 Normals	10 Inferior posterior infarctions		
	Mean and (S.D.)	Mean and (S.D.)	"t" value	Chance probability (%)
Maximum anterior voltage (MVA)	0 28 (0 14)	0 85 (0 27)	6 30	<1
Maximum posterior voltage (MVP)	0 468 (0 21)	0 525 (0 257)	0 6	N.S.
Anterior/posterior voltage ratio (MVA/MVP)	0 69 (0 46)	2 03 (1 28)	3 10	<1
Anterior QRS duration (MSA)	34 8 5 5	47 8 (6 18)	6 00	<1
Anterior accession time	22 3 (4 7)	31 5 (4 45)	7 74	<1
Horizontal plane vector directions				
20 msec.	58 5 (26 9)	83 6 (9 5)	5 55	<1
30-msec.	14 3 (17 0)	49 8 (17 1)	5 87	<1
40-msec.	343 3 (22 6)	26 9 (18 3)	6 52	<1
Maximum QRS	333 7 (24 9)	28 6 (19 5)	4 87	<1
Half-area	351 (15 3)	25 0 (12 4)	7 54	<1
Horizontal plane direction of maximum anterior voltage	50 6 (24 9)	47 0 (13 38)	0 60	N.S.

Means and standard deviations of 11 parameters of the anterior QRS forces in 70 normal subjects and in 16 patients presumed to hav[e] these groups combined

values for the eight significant parameters were selected which excluded 95 per cent of the normal subjects the diagnostic accuracy in dorsal infarction fell to completely unacceptable levels. Therefore multiple criteria were sought which in combination might accomplish what single criteria could not. This approach was suggested by Hugenholtz,[8] who proposed that voltage as well as the direction of the instantaneous vectors might be useful diagnostically in dorsal infarction Hoffman and associates,[19] in a study of inferior infarction, characterized some cases with unusually prominent anterior forces in terms of duration voltage and anterior posterior voltage ratio The specific values found were anterior voltage of 0.5 mv and anterior duration of 45 msec combined with an anterior posterior voltage ratio exceeding 1 These values correspond closely to the multiple criteria to be presented which are based on the study of entirely different patient populations.

In an examination of the eight significant parameters, it was apparent that several

*to have dorsal infarctions**

6 Pure posterior infarctions			*Combined group of all 16 posterior infarctions*		
Mean and (S.D.)	"t" value	*Chance probability (%)*	*Mean and (S.D.)*	"t" value	*Chance probability (%)*
0 74 (0 24)	4 39	1	0 81 (0 26)	7 94	<1
0 293 (0 21)	2 9	1	0 438 (0 245)	0 6	N.S.
3 00 (1 72)	2 98	1	2 39 (1 5)	4 25	<1
48 8 (15 9)	5 23	1	48 1 (6 03)	7 90	<1
35 4 (5 25)	5 46	1	34 9 (4 75)	9.32	<1
62 3 (15 7)	0 56	N.S.	75 6 (15 2)	3 36	<1
40 8 (12 9)	4 31	1	46 4 (16 2)	6 85	<1
28 0 (14 5)	6 36	1	27 3 (17)	8 31	<1
28 8 (8 55)	7 23	1	28 7 (16 3)	6 77	<1
27 8 (6 44)	10 86	1	26 0 (10 6)	10 59	<1
38 0 (11 3)	2 14	5	43 6 (14 6)	1 44	N.S.

dorsal infarctions. The result and significance of the "t" ... is given for dorsal infarcts, for dorsal plus inferior infarcts, and for

expressed the same phenomena. For example the prolonged duration of anterior forces in dorsal infarction may be expressed as milliseconds anterior as well as in the direction of the 30 and 40 msec. vectors. The simplest of these three to obtain is the total anterior duration since this can be measured on a high-fidelity Z axis lead alone The value selected was 42 msec.

The increased magnitude of the anterior forces is best expressed as the maximum anterior voltage achieved This value may also be determined from the high fidelity Z lead if the sensitivity has been standardized. The value selected was 0 5 mv., which is remarkably close to the anterior voltage criterion of 0.55 mv proposed by Wolff.[11]

Comparison of anterior with posterior phenomena is apparent in three parameters studied—the A/P voltage ratio the half area vector direction and the maximum QRS vector direction Of these three, the half area vector was selected Although this vector is weighted in favor of large fast-moving QRS forces and against smaller

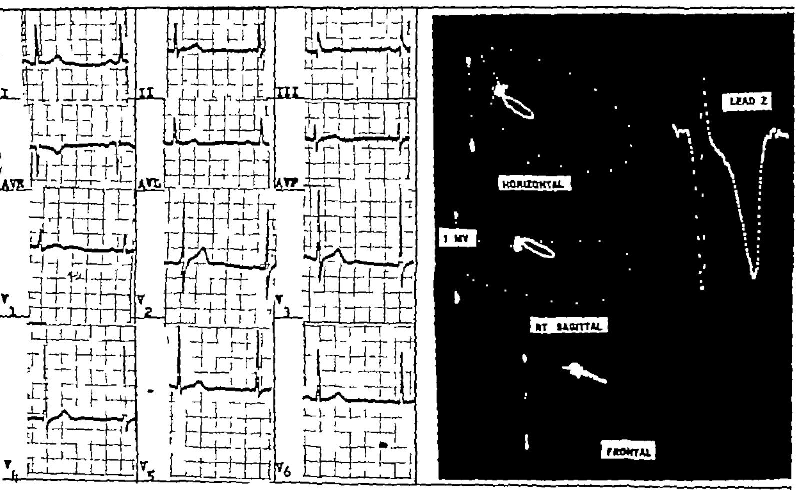


Fig. 3. Twelve-lead ECG and Frank system VCG of a 51-year-old male patient who had clinical acute myocardial infarction with progressively rising R and T waves in Leads V and V. The prolonged ascension time of the anterior forces is well shown in the Z lead.

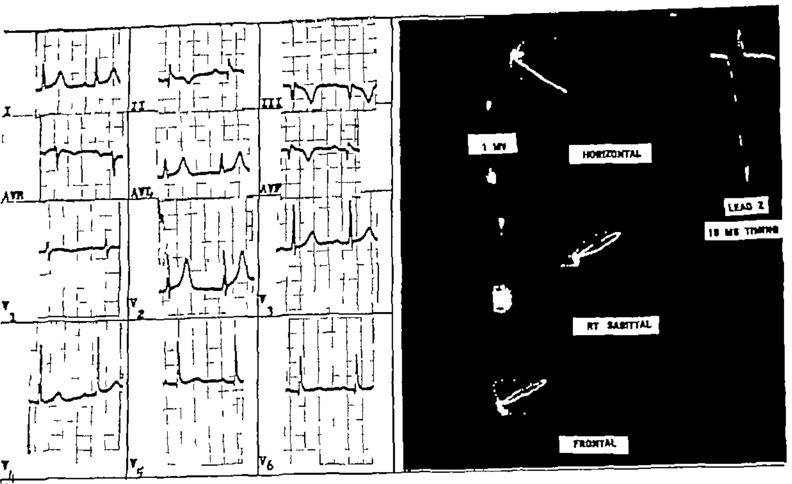


Fig. 4. The 12-lead ECG and Frank system VCG of a 32 year-old male patient whose serial electrocardiograms indicated inferior as well as dorsal infarction. The frontal loop is characteristic of inferior infarction. The horizontal loop, and the Z-lead, indicate the characteristics of dorsal infarction described in the text.

Table III. Statistical overlap of data on 8 parameters of the anterior QRS forces which were significantly different in normal subjects and in patients with dorsal infarcts

Milliseconds Anterior

Values	70 Normals		16 Dorsal infarcts	
+50			2	
50	1		5	
48	1		2	
45	4		4	
42	2		2	94
40	9	89%		
38	7		1	
35	15			
32	10			
30	13			
28	4			
25	4			

Max. Ant. Volt./Max. Post. Volt.

Values	70 Normals		16 Dorsal infarcts	
3.00+			3	
2.00–2.99	1		4	
1.50–1.99	2		1	
1.01–1.49	5		8	100%
1.00–	62	89%		

Anterior Accession Time

Values	70 Normals		16 Dorsal infarcts	
42			3	
40			1	
			1	
35			4	
	4		2	
30	5		4	94
	3	87%	1	
25	12			
	14			
20	17			
	7			
15	8			

Horizontal Plane Half Area Vector

Values	70 Normals		16 Dorsal infarcts	
+50's			1	
+40's			1	
+30's	3		4	
+20	2		6	
+10's	4		3	94%
+ 0's	12	87%	1	
− 0's	8			
−10's	20			
−20's	14			
−30's	6			
−40's	1			

Maximum Anterior Voltage

Values	70 Normals		16 Dorsal infarcts	
+0.90			5	
0.90	1		2	
0.80			2	
0.70	1		1	
0.60	2		2	
0.55			2	89%
0.50	2	91	1	
0.45	1			
0.40	5		1	
0.35	58			

Horizontal Plane Max. QRS

Values	70 Normals		16 Dorsal infarcts	
50's	1		2	
40's	1		3	
30's	2		2	
20's	3		7	87
10's	10	90%	1	
0's	12			
− 0's	13			
−10's	16		1	
−20's	6			
−30's	6			

Horizontal Plane 30 Msec. Vector

Values	70 Normals		16 Dorsal infarcts	
80's			1	
70's				
60's	1		4	
50's	2		2	
40's	4		3	
30's	7		5	100%
20'	12	80%		
10's	14			
0's	22			
− 0's	3			
−10's	5			

Horizontal Plane 40 Msec. Vector

Values	70 Normals		16 Dorsal infarcts	
50's			3	
40's	1		1	
30's	1		4	
20's	1		3	
10's	4		3	87%
0's	10	90%	1	
− 0's	8		1	
−10's	11			
−20's	18			
−30'	16			

The heavy line indicates the best separation possible. None of the 8 parameters alone provides satisfactory diagnostic criteria.

Table IV. Diagnostic results using 4 selected parameters of the anterior QRS forces singly and in combination for the identification of patients with dorsal infarct and the exclusion of normal subjects

Proposed criteria	*"False-positive" diagnoses in 70 normal subjects*		*"False-negative" diagnoses in 16 subjects with dorsal infarctions*	
	Number	*Per cent*	*Number*	*Per cent*
Maximum anterior voltage 0.5 mv. or more	6	8.6	1	6
Anterior accession time 30 msec. or more	9	12.8	1	6
Half-area vector 10 degrees or more anterior to 0-180 degree horizontal plane axis	~~8~~ 9	~~11.4~~ 13.0	1	6
Total anterior QRS duration 42 msec. or more	9	12.8	1	6
All 4 of abov criteria satisfied	2	2.8	2	13

slowly moving ones, it does provide a rough comparison of anterior time and voltage with posterior time and voltage.[14] Furthermore, the "f" test values using the half-area vector direction showed excellent separation of normal and patient groups. The value selected was a horizontal plane value for the half-area vector of at least +10 degrees.

Lastly the accession time of the anterior forces was included. The high "f" test values for this determination indicate that the anterior forces in patients with dorsal infarction in this series developed to peak values more slowly than did the anterior forces in normal subjects. The critical value selected was 30 msec. from QRS onset to peak anterior voltage achieved.

Table IV shows the results when these four criteria are applied singly or in combination to the 70 normal subjects and 16 patients with dorsal infarcts under study. It is readily seen that each criterion, when employed alone results in an unacceptably high number of false-positive diagnoses. However when all four criteria are used, the number of false positives falls to 2.8 per cent (2 of ,0 normal subjects). The diagnostic accuracy of the combination was 87 per cent (14 of 16 patients with dorsal infarct).

The high-fidelity Z-axis lead (Fig. 3) is an extremely useful tool in the diagnosis of dorsal infarction. This scalar representation yields accurate data on three of the four proposed criteria—accession time total anterior duration and anterior voltage. In addition, one can obtain from this lead the anterior-posterior voltage ratio which can be used as a fourth criteria if the QRS loops do not lend themselves easily to half area determinations.

The weakness of these criteria is that the diagnoses of dorsal infarction are not confirmed by autopsy. Although all patients accepted for study had clinical myocardial infarction and serially increasing R and T waves in the right precordial leads, this evidence is presumptive only. It is readily conceded, therefore, that the proposed criteria are approximations only and subject to review and modification as evidence accumulates.

Summary and conclusions

1. Twenty three patients with presumed dorsal infarction were studied with the Frank vectorcardiogram.

2. Six patients with "pure" dorsal infarction and 10 with dorsal infarction plus inferior infarction manifested normal horizontal and sagittal plane rotation.

3. No single parameter of all those measured, provided acceptable separation

between the 16 patients with dorsal in farction and the 70 normal subjects.

4. Specific values for maximum anterior voltage anterior QRS duration anterior accession time and horizontal half-area vector direction when all were present provided good separation of the 16 patients with infarcts from the 70 normal subjects

We wish to acknowledge statistical consultation with Dr Joseph B Chasm and the technical services of Sister Grace Isabel and Mrs Joan Gumowitz

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Corrected transposition of the great vessels without associated defects

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Corrected transposition of the great vessels is a congenital anomaly consisting of transposition of the origin of the aorta and pulmonary artery with inversion of the ventricles and the atrioventricular valves. This results in a functionally corrected transposition in which systemic venous blood enters the pulmonary artery and arterial blood enters the aorta. Unlike complete transposition of the great vessels, corrected transposition is a more benign condition, often compatible with long survival. Intracardiac shunts and other congenital anomalies are frequently present. Malformation of the "mitral" or left A-V valve produces a clinical picture of mitral insufficiency and is present in so high a percentage of cases as to form part of the syndrome.[1]

Ten cases of corrected transposition without associated defects or significant mitral insufficiency have been reported. Adequate clinical data are available in 6 of these cases, and this information is summarized in Table I. Fourteen cases of corrected transposition complicated only by mitral insufficiency have been described. Adequate clinical information is available in 8 of these cases and is summarized in Table II.

We report here 2 additional cases of corrected transposition in situs solitus hearts without associated congenital defects or significant mitral insufficiency. In both cases a cardiac lesion was suspected because of the presence of heart block.

In this report we have followed the suggestions of Honey[2] regarding terminology. Ventricles and atrioventricular valves are described as either left or right, depending upon their position in the body and not upon their morphology. Quotation marks are used when conventional terms are employed, i.e., the "mitral" valve or the left A-V valve.

Case reports

Case 1. D.M., a 9-year-old girl, was first noted to have a heart murmur and episodes of slow pulse at 3 years of age. The mother's pregnancy and delivery had been normal. The child's development was normal. In early childhood, easy fatigue was noted, especially at high elevations.

Physical examination at 9 years of age revealed a thin girl with a supine blood pressure of 130/60 mm Hg. The pulse was full, slow, and regular. Occasional prominent atrial waves were seen in the jugular pulse. A Grade 3/6, full systolic murmur was present along the left sternal border at the third intercostal space. A short, Grade 2, high-pitched decrescendo diastolic murmur was heard at the third intercostal space along the left sternal

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Table I. Clinical data on 6 patients with uncomplicated corrected transposition of the great vessels

Case No.	Age Sex	Symptoms	Murmurs	Second sound at pulmonic area	X-ray
1	11 M	None	Murmur for many years. Gr. 2/6 pulmonic systolic murmur. Gr. 4/6 diastolic murmur at LSB	Loud and single	Globular heart, prominent pulm. art. pulsations. Convex left superior border. Long impression on barium-filled esophagus
2.	8 F	Slight fatigue	Murmur noted at 1 month. Gr. 2/6 pulmonic ejection murmur	Loud and single	Central displacement of the heart. Straight left upper border. Esophagus displaced to right and posteriorly
3	3½, F	None	Gr. 2/6 pulmonic systolic ejection murmur	Loud and single. Early systolic click	Concave pulmonic segment
4	36 M	Sudden collapse with onset of heart block. Congestive failure	Gr. 2 apical systolic murmur	Louder than aortic second sound	Right and left ventricular enlargement. Hypoplastic aorta
5.	17 F	None	Heart murmur at 6. Gr. 2/6 systolic ejection murmur at 3rd IS, LSB	Loud and single	Narrow pedicle, globular heart. Right pulm. art. prominent. Long displacement of esophagus in PA view
6.	9 F	None	Heart murmur and periods of bradycardia at 3. Gr. 2/6 full systolic murmur 5th IS LSB. Gr. 2/6 short diastolic murmur at LSB	Loud and single. Systolic ejection click	Narrow pedicle. Globular heart. Right PA prominent. Long displacement of esophagus in PA view

*Cases previously reported by Grashoom[4] and Helmholz[5] are not included because of the lack of clinical data in these reports.

edge. Occasionally it was accentuated to a Grade 3 murmur. The second sound at the base was loud and single and the apical first sound was accentuated.

The electrocardiogram (Fig. 1) revealed complete heart block. The P waves were wide, slurred, and peaked, especially in Lead II. Q waves were absent in Leads aVL, V_5, and V_6. The mean frontal QRS axis was +10 degrees. Deep S waves were present in Leads V_1, V_2, V_3, and V_4. Deep Q waves or QS deflections were recorded in Leads III, aVF, and V_1. A tracing recorded when the child was 6 years old revealed similar features, with a first-degree heart block and a P-R interval of 0.24 second. The QRS complexes were unchanged and Q waves were absent in Leads aVL, V_5, and V_6 (Fig. 2).

Analysis of the phonocardiogram (Fig. 3) revealed a split first sound at the lower left sternal border. The following intervals were recorded: Q—"mitral" closure (left A-V valve) 0.04 second; Q—"tricuspid" closure (right A-V valve) 0.06 second. The "mitral" closure sound was faint, and the "tricuspid" sound was loud. A faint pulmonic component of the second sound was identified occurring 0.03 second after aortic closure during inspiration. Respiratory variation of this interval was normal. The diastolic murmur at the left sternal edge was slightly accentuated when atrial systole just preceded rapid ventricular diastolic filling. An ejection click was recorded at the base. It occurred 0.075 second after the Q wave. Occasional faint atrial sounds imitating a short murmur were recorded. Only slight variation in loudness of the first heart sound occurred with various P-R intervals.

Roentgenograms of the chest revealed moderate biventricular enlargement with a rounded cardiac apex (Fig. 5). The pedicle was narrow, the area of

*including data from 2 patients described in this paper**

Degree of A-V block	*Abnormal P waves*	*QRS axis (degree)*	Q_3 *(mm.)*	*Q aVF (mm.)*	*Pattern and deflection amplitude (mm.)* V	V	*Proof*	*Ref. No.*
0	+ Inversion in Leads II, III and aVF	−50	17	10	rSr 1/12/4	Rs 17/2	Cardiac catheterization and angiography	5
0	0	+60		0	RS 15/15	Rs 8/2	Cardiac catheterization and angiography	6
0	0	−30	15	8	RS 15/20	R 8	Cardiac catheterization and angiography	6
Complete	?	? Right ventricular hypertrophy		?	?	?	Autopsy	7
Complete	+	−80	10	8	QS 10	rs 3/1	Cardiac catheterization and angiography	Present paper Case 2
Complete	+	0	13	5	QS 13	R 8	Cardiac catheterization and angiography	Present paper Case 1

the main pulmonary artery was concave and long, slightly rightward displacement of the barium-filled esophagus was present. The aortic knob was not well seen. The pulmonary vessels were normal.

Right heart catheterization demonstrated no evidence of a shunt. The right ventricular pressure was moderately elevated. This may have been due in part, to the slow heart rate of 60 per minute (Table III). The pulmonary artery could not be entered. A 7-mm. "a" wave was present in the right atrium when atrial systole occurred during ventricular systole. The onset of the rise in pressure in the right ventricle occurred 0.04 second after the onset of the QRS. Brachial systolic pressures varied by less than 4 mm. Hg, with the usual varying relationship between atrial and ventricular systole seen in complete heart block.

Angiography was performed using 17 of 76 per cent Renografin injected into the right ventricle. The right ventricular chamber was smooth walled and the left ventricular chamber was trabeculated. The pulmonary artery was posterior and medial to its normal position (Fig. 7). The left A-V valves seemed to be slightly lower than usual, and persistent opacification of the left atrium suggested the presence of mild mitral insufficiency.

Case 2. R.R., a 17-year-old girl, presented for evaluation of a systolic murmur and a cardiac arrhythmia found on a routine examination 6 months previously. The mother's pregnancy and delivery had been normal. There was no childhood history of cyanosis, clubbing, or rheumatic fever. There were no cardiac symptoms, except some mild fatigue on effort during the past year. A faint heart murmur had been noticed at 6 years of age, but no subsequent notice had been made of a murmur until recently.

She was a normally developed, slim girl with a

Table II. Clinical data on 8 patients with corrected transposition of the great vessels and

Case No.	Age Sex	Symptoms	Murmurs	Second sound at pulmonic area	X-ray
1	17 F	Moderate limitation	Loud systolic murmur in 3rd IS LSB	Loud	Globular heart. Prominent right pulm. art.
2	26 M	Dyspnea on effort since childhood. Congestive failure	Apical syst. thrill and left ventricular heave. Gr. 6 full apical systolic murmur. Short soft apical diastolic murmur	Loud	Large right and left ventricle. Large left atrium. Long displacement of esophagus in PA view
3	7 M	Exertional dyspnea since birth	Syst. murmur at 4 yr. Gr. 4 basal systolic murmur. Longer Gr. 4 systolic murmur at apex. Short mid-diastolic murmur of low frequency	Loud, palpable, and single	Large heart. Straight upper left border
4	8 F	Moderate dyspnea and fatigue	Loud long systolic murmur and thrill at apex. Loud 3rd sound. Early diastolic murmur		Globular heart. Narrow pedicle. Prominent right pulm. art. Long displacement of esophagus in lateral view. LA enlargement
5	19 M	Slight disability in childhood more severe for past 3 mo.	Loud apical systolic murmur and thrill. Short low-pitched apical diastolic murmur. High-pitched early pulm. diastolic murmur. Heart lesion at 6 yr. Heart block 13 yr.	Loud and single. Pulm. systolic ejection click	Considerable cardiac enlargement and increased pulm. vascular shadows
6	19 M	Atrial fibrillation and heart failure 4 wk. previously	Heart murmur at 4 yr. Harsh apical systolic murmur. Loud 3rd sound and soft rumbling diastolic murmur	Accentuated palpable single second sound	Right and left ventricular enlargement, narrow pedicle, and pulm. congestion
7	4 M	Not stated	Not stated	Not given	Not described
8	8 M	No symptoms	Heart murmur at birth. Harsh Gr. 4 full systolic murmur 4th IS LSB and apex. Mid-diastolic rumble medial to apex. Loud second sound at pulm. area	Loud	Straight border in pulm. area

*Two cases described by [illegible] and one described by [illegible] are not included because of the lack of clinical data.

*mitral insufficiency reported previously**

Degree of A V block	Abnormal P waves	QRS axis (degree)	Q_1 (mm)	Q aVr (mm)	Pattern and deflection amplitude (mm) V	I	Proof	Ref No.
Complete	+	−15	3	2	rsr 1/5/4	RS 8/12	Cardiac catheterization	8
Complete	Atrial fibrillation	+80	2	0	RS 8/14	R 13	Cardiac catheterization and angiography	3
Complete	+	+60	5	4	QS 27	R 7	Cardiac catheterization	9
1st-degree P R = 0 22 sec.	+	−30	20	10	QS 20	RS 20/25	Cardiac catheterization and angiography	10
Complete	Atrial fibrillation	−70	8	10	QS 16	Rs 13/3	Necropsy	2
?	Atrial fibrillation				Complete LBBB		Necropsy	2
Complete	+	−70			QS 34	RS 9/12	Cardiac catheterization	1
1st-degree P R = 0.22 sec	+	0	7	3	rS 1/28	R 7	Cardiac catheterization nd angiography	20

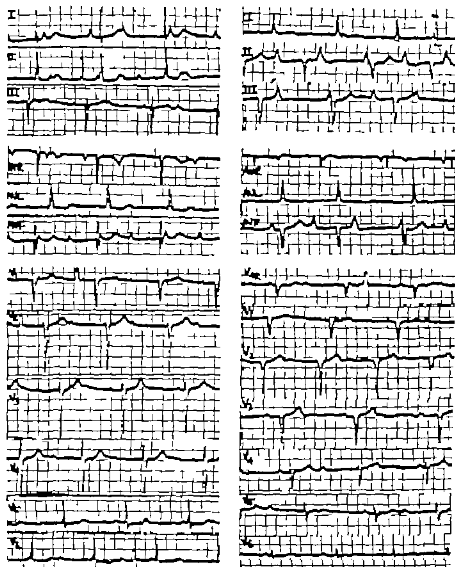


Fig. 1. Electrocardiograms of Case 1 (*left*) and Case 2 (*right*).

blood pressure of 140/80 mm.Hg. An irregular slow pulse was present with occasional prominent atrial waves in the jugular pulse. There was no abnormal precordial motion. A Grade 2/6 mid-systolic murmur was present at the third intercostal space along the left sternal border. The first sound at the apex was split. A loud single second sound was present at the pulmonic area. There was no diastolic murmur.

The electrocardiogram (Fig. 1) revealed complete heart block. Rare conducted beats occurred during the supernormal phase. The P waves were tall, wide, and notched especially in Lead II. Q waves were absent in Leads I, aVL, and V_6 in both conducted and nonconducted cycles. The mean frontal QRS axis was −55 degrees. Deep S waves were present in Precordial Leads V_1, V_2, V_3, V_4, and V_5. QS deflections were present in Leads II, III, and aV_F.

Analysis of the phonocardiogram (Fig. 4) revealed a split apical first sound. The following intervals were measured: Q—"mitral" closure (left A-V valve) 0.04 second; Q—"tricuspid" closure (right A-V valve) 0.09 second. The mitral closure sound was faint, and the tricuspid closure was the dominant component of the first sound at the apex and lower sternal edge. At the base, aortic valve closure was the dominant component, and it was followed by a faint sound of pulmonic valve closure which varied normally with respiration to a maximum A_2-P_2 interval of 0.03 second. A mid-systolic murmur of moderate intensity was recorded at the base. An ejection click preceded the murmur and began 0.12 second after the Q wave. Occasional faint atrial sounds were recorded. The first heart sound did not vary in the expected manner with variations in the P-R interval.

Chest roentgenograms (Fig. 6) demonstrated a

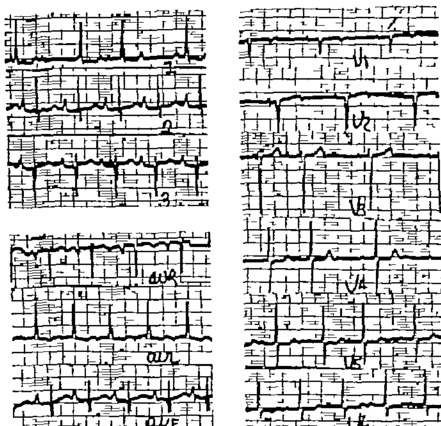


Fig. 2. Electrocardiogram of Case 1 at 6 years of age showing a prolonged P-R interval and occasional failure of conduction. Note absence of septal Q in Leads aVL, V5, and V6.

Table III. Summary of cardiac catheterization data in 2 patients with uncomplicated corrected transposition

Case 1			*Case 2*		
Sample site	*Pressure (mm. Hg)**	O_2 *content (ml./100 ml.)*	*Sample site*	*Pressure (mm. Hg)**	O_2 *content (ml./100 ml.)*
SVC		10.4	SVC		15.0
			IVC		16.0
RA	2	11.2	RA	0	15.7
RV	44/2	11.0	RV	1/0	14.9
			PA	18/3	15.3
BA	138/54	15.4	BA	142/80	19.4
BA saturation	97 per cent		BA saturation	98 per cent	
A-V difference	4.4 ml./100 ml.		A-V difference	4.1 ml./100 ml.	
O_2 consumption	140 ml./min.†		O_2 consumption	214 ml./min.†	
Cardiac index	3.5 L./min./M²		Cardiac index	3.3 L./min./M²	

*Referred to mid-chest.
†Assumed normal value.

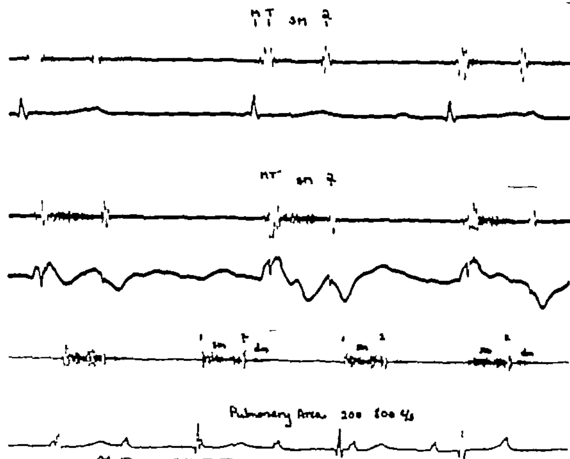


Fig 3 Phonocardiogram of Case 1 *Top* Tracing from the left sternal border *Middle* Apical sounds and apex impulse *Bottom* Record taken just below the pulmonic area at a frequency band between 200 and 800 cycles per second Note the early diastolic murmur reinforced by atrial systole (fourth complex from the left) Mitral closure (*M*)—left A V valve—precedes a loud sound of "tricuspid" closure (*T*)—right A V valve A systolic murmur of moderate intensity and a loud single second sound are present.

rounded apex a narrow pedicle a concave pulmonary conus, a slight prominence of the right pulmonary artery and a somewhat long rightward displacement of the upper portion of the barium-filled esophagus The aortic knob was not well seen.

Right heart catheterization demonstrated normal intracardiac pressures and no evidence of a shunt (Table III). The catheter followed a medial and posterior course to enter the left pulmonary artery Right atrial pressure tracings revealed a 10-mm a wave occurring during ventricular systole. The interval from the onset of QRS to the onset of the rise in pressure in the right ventricle was 0 06 second Inspection of the brachial arterial pressure trace revealed a variation of less than a 4 mm.Hg in systolic pressure between pulses occurring with the variable relationship between atrial and ventricular systole seen in complete heart block

Angiocardiography was performed using 50 c.c of 76 per cent Renografin injected into the right ventricle The right ventricular chamber was smooth walled The pulmonary artery was more medial and posterior than normal (Fig 8) The left ventricular chamber was trabeculated and the left ventricle formed the upper left border of the cardiac shadow instead of the infundibulum of the right ventricle No left A V valve insufficiency was detected.

Discussion

Mitral insufficiency is a common feature of uncomplicated corrected transposition. A mild degree of mitral regurgitation may be present in many instances as in Case 1 of the present report. It would seem to be logical therefore to include patients with mitral insufficiency in the group of cases of corrected transposition without associated congenital defects.

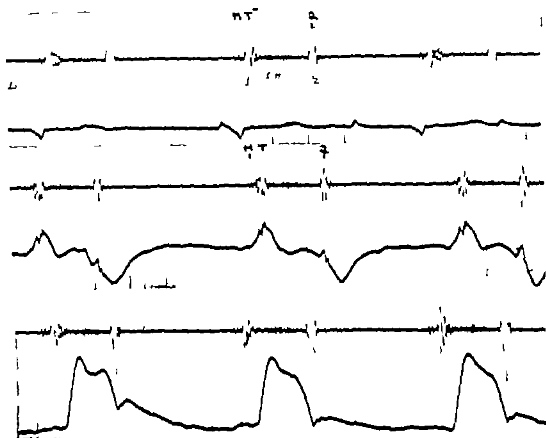


Fig. 4 Phonocardiogram of Case 2. *Top* Tracing recorded from the left sternal border *Middle* Apical sounds and apex impulse tracing *Bottom* Sounds from the left sternal border and the carotid impulse. Note "mitral"—left A-V valve closure (*M*)—preceding "tricuspid"—right A-V valve closure (*T*). A systolic murmur and a loud single second sound are present

Incidence Since patients without associated defects will usually be symptom-free, the true incidence of uncomplicated corrected transposition is probably higher than reported About 100 cases of corrected transposition have been reported or reviewed in the literature In the great majority there have been associated defects. Malers[3] reviewed 74 reported cases in 1960 In only 17 were there no associated shunts and in 13 of these "mitral" insufficiency probably due to a congenital defect of the left A-V valve was present Granboom[4] in 1891 was the first to describe corrected transposition without associated anomalies. No clinical details were reported Four cases have been described with adequate clinical information in regard to symptoms and physical signs.[5-7] Six cases of corrected transposition with associated mitral insufficiency have been reported with pertinent clinical information [1-4, 8, 19, 21] The details in both groups are summarized in Tables I and II

Embryology Since Rokitansky's[1] original description of the condition many embryological explanations have been proposed—by Harris,[12] Noonan [13] and Kernen [14] De la Cruz[15] proposed a mechanism which explains this complex malformation by the involvement of two embryonic elements—the bulboventricular loop, and the truncoconal septum As a consequence the aorta issues from the anatomic right ventricle in front of the crista supraventricularis. The pulmonary artery issues from the anatomic left ventricle. The ascending aorta runs parallel and ventral to the pulmonary artery Since the atria are structurally anchored they are in



Fig. 5 Case 1 Posteroanterior chest roentgenogram.



Fig. 6 Case 2 Posteroanterior chest roentgenogram

the anatomically normal position The abnormality is functionally corrected—the venous atrium is connected to the pulmonary artery and the arterial atrium is connected to the aorta. The possibility of abnormal timing or unequal distribution of the growth rates of the helically coiled primitive heart tube was pointed out by Grant[18] in 1964. This could produce the so-called polarity disturbances, including corrected transposition of the great vessels. The above-mentioned theory would seem to be applicable to Harris and Farber s transposition variants also.[12]

Anatomic features The special anatomic features resulting from the abnormal embryological development have been reviewed [8, 17] Common associated defects consist of ventricular septal defect, atrial septal defect pulmonary stenosis, patent ductus arteriosus, and coarctation of the aorta. In many cases mitral insufficiency may be due to a derangement of the insertion of the left A V valve similar to that seen in Ebstein s anomaly In other cases an anomalous insertion of the chordae may be responsible [4]

A cleft leaflet may also produce valvular insufficiency Complete inversion and transposition of the coronary arteries is usually present.[1, 4] There is also inversion of the conduction system so that the anatomic left bundle takes a longer path from the A V node to the ventricular septum probably accounting in part for the high frequency of heart block. Walmsley [18] however noted fibrosis in the region of the bundle of His in his case.

Symptomatology Symptoms in patients with corrected transposition are due to the associated congenital defects. In patients without associated congenital defects, symptoms are due either to complete heart block or to associated mitral" insufficiency Complete heart block appears to be well tolerated in childhood but its sudden appearance in an adult may well precipitate congestive failure (Case 4 Table I) Although mitral insufficiency may be a late complication related to the structural weakness of the left A V valve congenital deformities of the mitral valve are probably responsible for serious associated mitral insufficiency in infancy and childhood

With reference to Tables I and II it can be seen that 7 of 14 patients had symptoms. Four of the 7 had complete A V block and mitral insufficiency 2 had mitral insufficiency without complete block, and 1 patient without mitral insufficiency had cardiac symptoms at the age of 36 when complete A V block appeared In the absence of associated congenital defects or significant mitral insufficiency corrected transposition is probably an asymptomatic lesion in the early years, even in the presence of heart block.

Diagnosis The diagnostic features of



Fig. 7. *Above:* Enlarged view from cineangiocardiogram of Case 1 showing injection into the right ventricle and filling of the pulmonary artery in the left anterior oblique view. The anterior chest wall is to the left and the spine to the right. Note the posterior position of the pulmonary artery and the smooth outline of right ventricle. *Below:* Similar view from cineangiocardiogram of Case 1 a few seconds after the view shown above. The left atrium, left ventricle and aorta are now seen. Note the anterior position of the aorta in relation to the pulmonary artery and trabeculations of the left ventricle.



Fig. 8. Lateral view of selective angiogram of Case 2. *Above:* The pulmonary artery is seen in its posterior location. *Below:* The aorta is seen in its anterior position.

corrected transposition have been reviewed by Honey.[3] In the absence of heart block or mitral insufficiency the physical findings may not be striking. The apex impulse may be forceful and a left parasternal heave may be present. The most common finding is a loud single often palpable second sound at the upper left sternal edge. A systolic ejection murmur and an ejection click may be present in this area. These signs, together with an electrocardiogram that does not demonstrate right

ventricular hypertrophy and an x-ray silhouette that reveals a globular heart with a narrow pedicle should raise the suspicion of uncomplicated corrected transposition When A V block is present a slow pulse and cannon a waves will be seen in the neck The first heart sound may vary its intensity but this was not a prominent feature in the 2 cases described in this paper When mitral insufficiency is significant, a full apical systolic murmur will be present and often an early rumbling diastolic flow murmur

The loud single second sound ejection click, and systolic ejection murmur at the base probably arise in the aorta which lies close to the chest wall Systolic murmurs at the apex and lower sternal edge are probably due to varying degrees of mitral insufficiency or are related to the slow heart rate when complete A V block is present Transmission of systolic mitral murmurs to the chest wall to the left of the sternum is probably facilitated by the greater proximity of the left ventricle and left atrial appendage to the chest wall in this area. A diastolic murmur at the left sternal border is often present even in the absence of significant mitral insufficiency [2,4] This was also observed in Case 1 Such murmurs may be due to a minor degree of aortic insufficiency or they may be flow murmurs of mitral origin Transmission to the chest is probably facilitated by the abnormal position of the aorta and left ventricle It is possible that the abnormal torsion of the root of the aorta and the structure of the left ventricular outflow tract may produce a minor degree of aortic insufficiency Abnormal precordial heaves are probably due to the left ventricle lying closer beneath the rib cage than normal and thus transmitting its more forceful impulse to the chest wall

The electrocardiogram is most helpful in the diagnosis of corrected transposition Complete A V block occurred in 60 per cent of reported cases of corrected transposition in patients without other congenital defects (Tables I and II) Indeed the presence of complete A V block in a child or young adult should raise the possibility of corrected transposition Nakamura and Nadas [19] in their report of 61 instances of heart block in infants and children included 5 patients with corrected transposition

Other important electrocardiographic features are tall wide notched P waves especially in Lead II left axis deviation deep S waves in the precordial leads, deep Q waves in Leads III and aV$_F$ absence of the normal septal Q wave in Leads V$_6$ and aV$_L$ and absence of the corresponding initial upward R wave in Lead V$_1$ In place of the usual small q wave in Lead V$_6$ a slightly slurred initial portion of the R wave is present which appears to be quite characteristic. Of all the electrocardiographic signs, A V block abnormal P waves, and absence of septal Q waves were the most common in the cases summarized in Tables I and II Absence of Q waves in Leads I aV$_L$, V$_5$, and V$_6$ appears to be a distinct electrocardiographic abnormality It has been encountered in only 0.48 per cent of 408 normal children in a recent study [22]

The phonocardiogram is helpful in identifying the single second sound at the pulmonic area as being due to aortic valve closure and the ejection click as being an aortic ejection click Usually a faint sound of pulmonic closure can be identified especially at the aortic area.[21] The order of valve closure appears to be unaltered as judged from the phonocardiograms of the 2 patients described in this paper Left A V valve closure occurs before right A V valve closure This suggests that the left ventricle initiates its contraction first as in normal subjects, despite the reversal of the conduction system It should be noted that in the presence of complete A V block, the pacemaker may be so located as to facilitate early left ventricular depolarization In occasional conducted beats during the supernormal phase in Case 2, however the order of valve closure remained unchanged

Cardiac roentgenograms in cases of uncomplicated corrected transposition may demonstrate several suggestive signs. The heart may have a globular shape with a rounded apex. The pedicle is thin with an inconspicuous aortic arch and the left upper border is straight or convex because of the medial position of the pulmonary artery For the same reason the right pulmonary artery may be prominent The

pressure of the posteriorly placed pulmonary artery may produce a long rightward displacement of the barium-filled esophagus in the posteroanterior view and posterior displacement at the same level may be seen in lateral views. When mitral insufficiency is present, left atrial and left ventricular enlargement may be present.

The diagnosis of corrected transposition is best confirmed by selective angiography with an injection into the right ventricle or right atrium. The medial and posterior placement of the pulmonary artery is best seen in posteroanterior and lateral views. The right ventricular chamber will be smooth walled without trabeculae or a crista supraventricularis. The left ventricle will demonstrate these features. A left ventricular injection of contrast medium will best demonstrate this abnormal appearance of the left ventricle and also enable one to detect the presence of associated "mitral" insufficiency.

Cardiac catheterization is helpful in excluding the presence of associated congenital defects and in assessing the hemodynamic importance of associated mitral insufficiency. If the catheter can be advanced into the pulmonary artery, a medial course and a posterior position in the outflow tract and main pulmonary artery can be documented by posteroanterior and lateral spot films.

These general points are in agreement with those made by Schiebler[1] and his workers at the Mayo Clinic who have reviewed 33 cases of corrected transposition. Three had no additional anomalies, except mitral insufficiency. One patient had no associated anomalies and did not have mitral insufficiency. Three of these 4 cases have been reported elsewhere.

Prognosis. The prognosis in corrected transposition without associated congenital defects is probably good even in the presence of heart block appearing in childhood. In adults, heart block may precipitate congestive failure. When associated congenital lesions or mitral insufficiency are severe, the prognosis is correspondingly worse. Of 10 cases of uncomplicated corrected transposition reported by Cumming, were diagnosed at autopsy. Three of these patients died of diseases not related to their congenital anomaly, data are not available in 2 patients, and 1 patients died at 35 and 36 years of age with heart block of 10 and 11 years duration, respectively. Of 6 patients with associated mitral insufficiency, 2 died at 31 and 50 years of age. One of these patients died of heart failure, and the other of nonspecified disease. It is not known whether either patient had heart block. Supraventricular arrhythmias may occur frequently, especially atrial fibrillation, but are usually not of serious consequence.[1]

Since mitral insufficiency and heart block can be effectively treated at the present time by valve surgery and the employment of an implanted pacemaker, respectively, the ultimate prognosis of patients even with these complications is much more hopeful. Still unanswered, however, is the question of whether the right ventricle subjected to systemic work loads for many years would for this reason alone fail at an earlier age.

Summary

Two patients with complete atrioventricular block and corrected transposition of the great vessels without intracardiac shunts have been described. One patient had mild associated mitral insufficiency. The diagnosis is difficult in uncomplicated cases, which probably accounts for the paucity of case reports of this interesting syndrome. The prognosis is good. The diagnosis should be suspected in children or young adults when heart block or congenital mitral insufficiency is present. In the absence of these findings, an x-ray silhouette demonstrating a globular heart with a narrow pedicle, an electrocardiogram with abnormal P waves and absent septal Q waves, together with the presence of a loud single second sound at the pulmonic area, are important additional diagnostic clues.

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Systolic clicks and the late systolic murmur

Intracardiac phonocardiographic evidence of their mitral valve origin

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High frequency clicking sounds occurring in mid or late systole have generally been considered to be extracardiac. In 1913 Gallavardin[1] described systolic clicks in 3 patients who had pericardial adhesions at autopsy, and subsequent investigators have largely supported the point of view that these sounds originate in the pericardium or contiguous extracardiac structures.[2-6] Additional evidence bearing on the extracardiac source of systolic clicks relates to their occurrence with mediastinal emphysema,[7] pericarditis,[8] and pneumothorax,[9] their occurrence as part of the "xyphosternal crunch,"[10] and their apparent synchrony with pericardial tugging seen at fluoroscopy.[2] The benign natural history of patients with isolated systolic clicks has added weight to the contention of their innocence.

Late systolic murmurs which are devoid of audible or recordable early systolic vibrations have also generally been considered to be extracardiac and, hence, benign.[4,5,11-13] The paucity of additional clinical evidence of heart disease in many of these patients is consistent with this point of view. Pericardial origin of late systolic murmurs is in some instances supported by a history of pericarditis and by typical T wave changes in the electrocardiogram.[4] In addition, late systolic murmurs frequently coexist with systolic clicks, which suggests that both might share a common origin. Because of Gallavardin's proposal associating systolic clicks with previous pericardial disease, one of us (W. P. H.) has for the past 18 years made a careful search for this association. Occasionally there appeared to be a relationship, but in the great majority of patients a complete cardiovascular evaluation (including a detailed history, physical examination, electrocardiogram, and x-ray and special laboratory data) failed to disclose evidence of pericardial disease. Accordingly, the clinical impression evolved that the systolic click (not to be confused with the "ejection sound" or "ejection click") was not usually related to pericardial abnormalities, but instead had a different, although as yet obscure, etiology. Nevertheless, the click appeared to represent a benign auscultatory finding. The same observations were applied to the late apical systolic murmur

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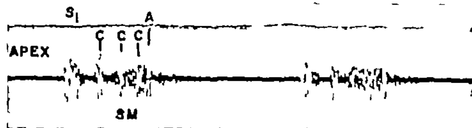


Fig. 1. Phonocardiogram at the cardiac apex. The late systolic murmur (*SM*) begins shortly after the first of three clicks (*C*) and continues up to the second of aortic valve closure (*A*). The interval between the first heart sound (S_1) and the initial click is devoid of murmur.

which generally appeared to be clinically benign and which sometimes was associated with a systolic click (or clicks). However, occasionally a patient with a late apical systolic murmur had definite autopsy evidence of rheumatic mitral insufficiency and rarely this murmur was detected in a patient with a calcified mitral annulus which was believed to be causing mitral regurgitation. The clinical association of the late apical systolic murmur with pericardial disease has not been observed in our previously studied cases.

Recent evidence based on left ventricular angiocardiography has convincingly demonstrated mitral incompetence in some patients with late systolic murmurs,[6,11,14] and intracardiac phonocardiography has detected the murmur in the inflow tract of the left ventricle.[14] Furthermore, the response of the late systolic murmur to vasoactive drugs is similar to the response of the pansystolic murmur of mitral regurgitation.[12,13]

However, simultaneous intracardiac registration of both the late systolic murmur and the systolic clicks in the same patient with hemodynamic evidence of organic mitral incompetence has thus far not been reported. The purpose of this study is to describe observations which appear to provide these data.

Case Report

The patient was a 23-year-old white woman who had a history of a murmur since the age of 2 years. She was asymptomatic, except for intermittent episodes of paroxysmal rapid heart action. Right heart catheterization performed at the age of 17 years was reported to be normal.

Physical examination. The blood pressure was 115/65 mm. Hg. The cardiac rate was 74 per minute and the rhythm was regular. The arterial pulse and the jugular venous pulse were normal. Examination of the chest revealed a loss of normal thoracic kyphosis. The cardiac apex was identified as a gentle left ventricular tap in the fifth intercostal space at the mid-clavicular line. A systolic thrill was localized at this point. Auscultation at the apex revealed a normal first heart sound, two or more mid to late systolic clicks, and a Grade 4 (out of 6) late systolic murmur which enveloped the sound of aortic valve closure (Fig. 1). The murmur radiated to the axilla and to the angle of the left scapula. A third heart sound was not audible. At the pulmonary area the second sound remained closely split during expiration but widened normally during inspiration. The intensity of the two components was equal.

The electrocardiogram was normal. Evidence of left atrial enlargement was not apparent in the *P* waves.

The chest x-ray film revealed a normal cardiac silhouette and the barium esophagram provided only equivocal evidence of an increase in left atrial size.

Method of Investigation

Percutaneous right heart and transseptal left heart catheterizations were performed by way of the right saphenous vein. The hemodynamic data are contained in Table I.

In addition to the foregoing information the following phonocardiographic observations were made using Sanborn 550M or 546 polybeam photographic recorders. A left atrial intracardiac phonocardiogram was recorded simultaneously with a left atrial pressure pulse by attaching the Dallons-Telco* external micromanometer to the transseptal catheter. A late systolic murmur and two or more systolic clicks were detected just above the mitral orifice (Fig. 2). When the catheter was withdrawn from the left atrium into the right

*Manufactured by the Dallons Laboratories, Inc., 5066 Santa Monica Blvd., Los Angeles 29, Calif.

Table I Hemodynamic data

			Control		*Pressor amine*	
Site }	*Right atrium*	*Right ventricle*	*Brachial artery*	*Left atrium*	*Brachial artery*	*Left atrium*
Pressure (mm. Hg)	a waves 3	Systolic 18	Systolic 98	a wave 10	Systolic 138	a wave 17
	v waves 1	Diastolic 2	Diastolic 55	wave 9	Diastolic 80	v wave 21
	Mean 2		Mean 69	Mean 7		

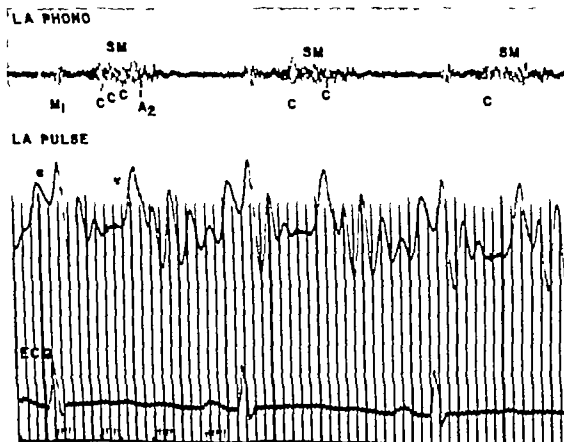


Fig. 2. Intracardiac phonocardiogram recorded from within the left atrium (LA). The systolic murmur (SM) begins just before the first click (C) and continues up to the sound of aortic valve closure (A2). The left atrial pulse and electrocardiogram are simultaneously recorded.

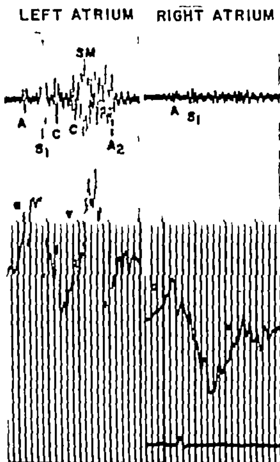


Fig. 3. Intracardiac phonocardiogram and simultaneous pressure pulses recorded as the catheter was withdrawn from the left to the right side of the interatrial septum. The systolic click (*C*) and late systolic murmur (*SM*) were grossly apparent within the left atrium but were absent within the right atrium. Note the decline in *a* and *v* waves of the atrial pressure pulses as the catheter traversed the septum. *A*, Atrial sound. *S*, First heart sound. *A*, Aortic valve closure.

atrium, the murmur and the clicks abruptly disappeared as the septum was traversed (Fig. 3).

Prior to removal of the left atrial catheter, the following pharmacologic observations were made. Control tracings included left atrial and brachial arterial pressure pulses, together with an electrocardiogram and a thoracic wall phonocardiogram from the cardiac apex. Aramine bitratrate was then infused intravenously until the brachial arterial systolic pressure rose from 98 to 138 mm. Hg. The left atrial *v* wave rose from 9 to 21 mm. Hg, and the late systolic murmur and systolic clicks became markedly amplified. Early systolic vibrations remained absent (Fig. 4).

Subsequently, additional phonocardiograms were recorded from the cardiac apex and third left intercostal space before and after the patient inhaled amyl nitrite for 10 seconds (Fig. 5). At 20 seconds the late systolic murmur had appreciably diminished. At 30 seconds the systolic clicks had markedly diminished. At 50 seconds the late systolic murmur was still less than the control level, but early systolic vibrations had appeared.

Discussion

Identification of the origin of the late systolic murmur in this study was based upon hemodynamic and phonocardiographic responses to vasoactive drugs, as well as upon the diagnostic reliability of intracardiac phonocardiography. The increased resistance to left ventricular discharge associated with the infusion of pressor amine caused an acute increase in mitral regurgitant flow that was reflected in the significant increase in the left atrial *v* wave.[16] As the *v* wave rose, the late systolic murmur became markedly amplified[16] (Fig. 4), a response characteristic of mitral incompetence.[17,18] Despite the elevated pressure on the ventricular side of the mitral leaflets, early systolic vibrations remained absent.[11] On the other hand, the decreased resistance to left ventricular discharge caused by the inhalation of amyl nitrite resulted in an acute decrease in regurgitant flow and a decline in the intensity of the late systolic murmur (Fig. 5), a response also typical of mitral regurgitation.[16,17,19] The appearance of early systolic vibrations in the postinhalation phonocardiogram is a point of interest[8] which has no ready explanation. It was of further interest that the systolic clicks became amplified after the infusion of Aramine and became softer after the inhalation of amyl nitrite in a fashion analogous to the late systolic murmur (Figs. 4 and 5). However, the decreased intensity of the clicks after amyl nitrite appears to be inconstant,[11] and sudden disappearance of the clicks after injection of pressor amine appears to be common.[8]

The diagnostic value of intracardiac phonocardiography in this study was based

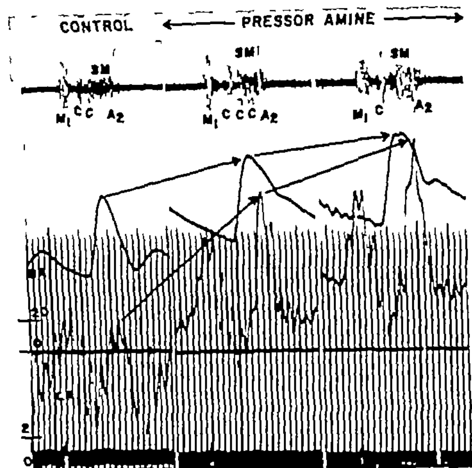


Fig. 4. Simultaneous apex area phonocardiogram, brachial arterial pressure pulse (*BA*), and left atrial pressure (*LA*) before and after intravenous infusion of Aramine bitartrate. The BA systolic pressure rose from 98 to 120 to 138 mm Hg. The LA v wave (*lower arrow*) rose from 9 to 16 to 21 mm Hg. The late systolic murmur (*SM*) became markedly amplified. The clicks initially increased in intensity (*middle tracing*). The first click remained loud, but the latter two were ultimately lost within the murmur (*right tracing*). *M*, Mitral valve closure. *A*, Aortic valve closure.

upon observations[19] that cardiac murmurs can often be localized to the chamber or vessel that receives the flow of blood responsible for their production. Detection of the late systolic murmur within the left atrium (Fig. 2) together with prompt disappearance of the murmur on the right side of the atrial septum (Fig. 3) constitute substantial evidence that the murmur originated at the mitral orifice. The intracardiac localization of the systolic clicks was identical with the localization of the late systolic murmur (Fig. 2), which suggests that the clicks also originated at the mitral orifice. Absence of the clicks within the right atrium was not only consistent with the foregoing thesis but also added weight to the evidence that they were not merely transmitted from extracardiac structures. Although this information does not permit conclusions as to which structural components of the mitral apparatus give rise to the clicks, the observations are in accord with proposals that mid or late systolic clicks may be produced in abnormal chordae tendineae[14] as their tension is abruptly altered during ventricular systole.[21] Indeed the term "chordal snap" has been coined to describe the click.[21]

A pansystolic murmur is the hallmark of mitral insufficiency. Although it has been recognized that these murmurs may have soft early systolic vibrations which

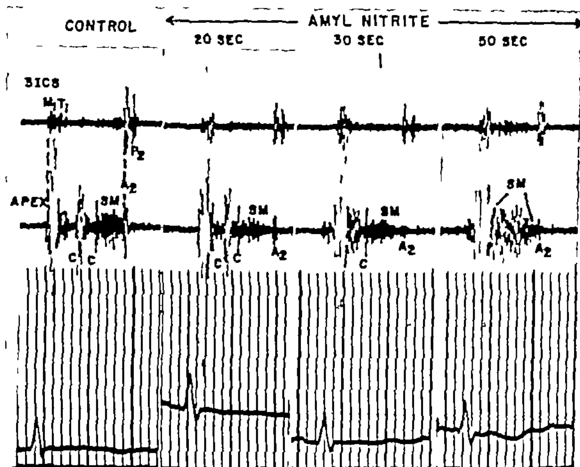


Fig. 5. Simultaneous phonocardiograms from the third left intercostal space (*3 ICS*) and the cardiac apex before and after 10-second inhalation of amyl nitrite. At 20 seconds the late systolic murmur (*SM*) has appreciably decreased, and the clicks (*C*) have become earlier. At 30 seconds the murmur remains softer, the second click has vanished, and the first click is markedly diminished. At 50 seconds the murmur becomes pansystolic even though the late systolic components remain soft.

rise to a late systolic crescendo.[17] It has generally been believed that pure late systolic murmurs are innocent, especially when accompanied by mid or late systolic clicks.[4-6] Both of these acoustical events have been considered to be extracardiac, originating in the pericardium or contiguous structures.[5,6] More recently, mitral incompetence has been convincingly demonstrated by left ventricular cineangiocardiography in some patients with late systolic murmurs.[4,12,13] Indeed, the regurgitation was believed to be confined to latter systole in these patients.[12,13] Systolic clicks occurred in four instances in one group[13] and late systolic murmurs were recorded in the inflow tract of the left ventricle in another group.[14] Furthermore, it has been observed that the response of the late systolic murmur to vasoactive drugs is similar to the response of the classic pansystolic murmur of mitral insufficiency.[12,20] The observations herein reported constitute additional evidence that both the late systolic murmur and the systolic clicks can be intracardiac events associated with organic mitral incompetence. In our case, as well as in those previously observed, the hemodynamic degree of regurgitation was mild.[11,13] Although the combination of left atrial localization of the late systolic murmur and clicks and the appropriate responses to vasoactive drugs constitutes convincing evidence that these auscultatory events can be associated with mitral insufficiency, the data do not imply that all late systolic murmurs and clicks are intracardiac. However

these observations do support the point of view that a late systolic murmur—either alone or together with clicks—can no longer uniformly be considered to be benign. Even though the magnitude of regurgitation is likely to be mild in such cases, the lesion is, nevertheless, likely to be susceptible to endocarditis.[15]

Summary

The use of intracardiac phonocardiography has been employed as a method of documenting the origin of systolic clicks associated with an isolated late systolic murmur in a patient with hemodynamic evidence of mitral incompetence. Registration of both of these acoustical events within the left atrial chamber has not been hitherto described. Response of the clicks and murmur to the infusion of pressor amine and to the inhalation of amyl nitrite adds further weight to the concept of their origin at the mitral orifice. These observations confirm and extend previous information relating the late systolic murmur to organic mitral incompetence even if the murmur is accompanied by systolic clicks.

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Diagramming and grading heart sounds and murmurs

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A great deal more information can be elicited by systematic auscultation of the heart than can be learned when only the usual gross findings are expressed by written description. This communication presents a system of notation which allows much more detail to be recorded in an efficient and easily understood manner. It also serves as an educational aid, since it demands that the student record every feature of the sounds and murmurs that cardiologists have found to be useful.

In 1933, when H. N. Segall described a graphic method for illustrating auscultatory findings, he offered it not only as a means of keeping records as conveniently and efficiently as possible, but also as a means of teaching and learning careful auscultation. He drew a picture of a rib cage in the center of a sheet of paper and had pointers going to the site of placement of the stethoscope and leading to a line of faintly outlined rectangular columns representing the heart sounds of one cycle. High-frequency and low-frequency murmurs were designated by the degree of separation of lines as in an actual phonocardiogram. Amplitude was graded by filling in the columns and drawing in the murmurs with relatively different heights. He had separate lines for the findings in different body positions, such as sitting, supine, and left lateral decubitus, all three of course only at the apex. In 1959[2] he modified his graph by additional features: symbols for bell or diaphragm, a rate scale, a place for the blood pressure, a corner footnote explaining the frequency symbols, extra lines to use for various body positions, and a split top to the first heart-sound rectangle to indicate the normal splitting of the first sound.

It was so effective in saving time that he could show that one such diagram was equal to a 629 word description of the auscultatory findings in a patient with aortic and mitral disease. The graph told the story at a glance, once you understood the symbols.

Such diagrams are valuable not only as records, but as self-teaching aids in training for auscultation, because if the examiner tries to fill in a graph, it forces him to listen carefully and separately to each component of the cycle. It is well known that this is the hallmark of the good auscultator. This was pointed out by Segall and recognized by Ravin,[4] who in 1958 modified Segall's schema to give even more information in keeping with advances in auscultation. He added the grading of murmurs from 1 to 6 by putting a number over the murmur, and he showed a method of representing medium-fre-

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quency murmurs. He kept Segall's method of determining the size of the heart sound blocks in the form of a footnote with blocks of certain heights, which he called "standards for normal sounds at the apex," which means the loudness of "normal" heart sounds by which to compare the heights of all the other heart-sound rectangles. An improvement in the above mentioned method of grading heart sounds seemed to us to be mandatory and stimulated us to construct an improved graph.

If these diagrams are to go on a patient's hospital chart, every physician from intern to orthopedic consultant ought to find it simple enough to be able to instantly understand the symbols with no text for explanation. With this in mind we have evolved a graphic method based on Segall's format but with the elimination of all words or symbols that could cause difficulty in understanding the meaning of the diagram. We shall also show how the graph can be used to teach improved methods of grading sounds and murmurs.

We found that triplicate areas for heart sound columns showing the areas of auscultation in different body positions were confusing. We would like to show why it is not necessary to draw the auscultatory findings for three body positions at the apex. Physicians customarily only describe murmurs in the position in which they are heard loudest, e.g., if we say that a diastolic murmur is Grade 4 at the apex in the left lateral decubitus position we do not wish to know in what position it was Grade 3 at the apex. By using multiple

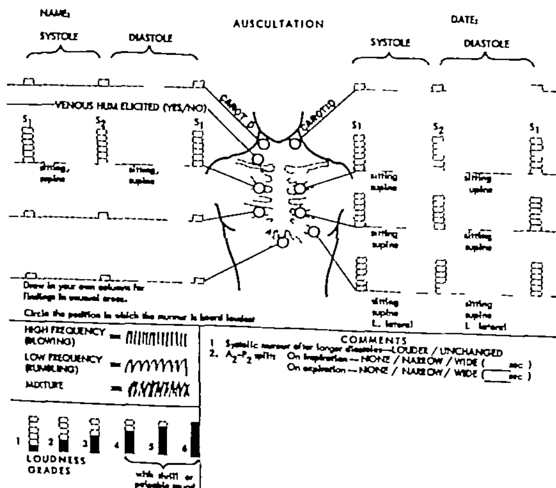


Fig. 1. See text.

choice words for sitting, supine, and left lateral under the diagram, one may indicate the position in which that particular murmur was loudest (Fig. 1).

We also believed that we were justified in eliminating symbols for the bell or diaphragm when we realized that it is unnecessary to tell anyone today that the low-frequency murmurs are heard best with the bell, the high-frequency murmurs with the diaphragm, and the mixed frequencies with either. If he does not know this, he probably would not appreciate the bell and diaphragm symbols anyway.

To further simplify the diagram we leave out both blood pressure and heart rate. Blood pressure is better recorded separately in space adequate for making notation of the values for both of the arms as well as for the legs in a section that describes peripheral pulses in detail. Heart rate is worth mentioning only if it is different from that in the cardiogram, which of course will routinely accompany every cardiac workup.

We use Segall's widely spaced wavy lines for low frequencies, and his closely spaced lines for high frequencies because they do resemble the way in which a phonocardiogram shows them. We believe, therefore, that anyone who has ever seen a phonocardiogram understands them immediately. But we add Ravin's[3] idea of medium or mixed frequencies too, although by a different method: low-frequency wavy lines plus diagonal lines through them. Segall's idea of a corner footnote on each diagram explaining the frequency symbols is still necessary.

Ravin's method of grading by putting a fraction out of 6 above each murmur (also suggested by Leatham) is an advance over only relative height for accuracy, but drawing murmurs of different heights still is, in our opinion, the quickest way of displaying relative as well as absolute differences in loudness. It is analogous to the difference between looking either at a complicated column of numbers or at a simple bar graph.

We also recommend grading amplitude on a scale of 6, but only if a more acceptable method of separating the grades is adopted than that in general use. When Freeman and Levine[6] in 1933 introduced the grading of murmurs up to 6, only Grades 1, 2, and 6 were described in detail. Grade 6 was a murmur heard with the stethoscope off the chest, and Grade 1 could be missed on first applying the stethoscope. Grade 2 was an easily heard faint murmur. By 1959 Levine[7] had proposed that Grade 5 could be heard with the edge of the chest piece on the chest. But he left the distinction between Grades 3 and 4 to be solved by the listener and gave no helpful verbal description. This handling of moderately loud murmurs was too much for many of our best cardiologists, including Paul Wood, who carried the 4-grade method to its fullest, probably because he thought it was easier to get agreement for soft, moderate, loud, and very loud. But that 4 grades was only a compromise that did not adequately classify the many amplitudes heard by good auscultators is easily seen by anyone who uses 6 grades, for he soon finds that he would like to use one-half grades for those between the usual 6. A better standardized and adequate system of grading was needed instead of giving up numbered grading altogether as some have done.

When we tried to teach the grading of murmurs out of 6, we found that it was easy to get agreement on what Grades 1, 2, 5, and 6 murmurs were when we used Levine's well-publicized concepts.[7] But when we tried to get agreement on Grades 3 and 4, we thought at first that it would be impossible because they were both loud murmurs with only some subtle differences between them. We finally solved this problem by using the thrill as a means of separating them; that is, if the moderately loud murmur was accompanied by a thrill, it was Grade 4. Although this made it easy for the students to grade murmurs, there was an objection to this system in that, since the threshold for the appreciation of thrills requires low frequencies at the amplitudes usually found in heart murmurs, it appeared to be possible that high-frequency murmurs may be very loud and not become palpable. But in actual experience the two typical high-frequency murmurs, those of aortic insufficiency and mitral regurgitation, have thrills associated with them often enough to convince us that, when these murmurs

get loud enough, they acquire low frequencies. In 1959 Bruns[9] helped to explain this phenomenon when he showed that, according to the vortex theory of the production of murmurs, high pitched murmurs due to small orifices acquire low frequencies as the orifice enlarges or becomes less circular. They may also acquire low frequencies if the stethoscope is placed in the direction of flow, i.e., downstream from the source of the murmur. He explains this by the area of vortex coalescence being downstream from the source of the murmur.

It is true that theoretically two loud sounds of different frequencies may appear to be equally as loud in decibels and only one may have a thrill,[8] and that this is true if the "loud" sound is the one with the high frequencies, as in aortic insufficiency. But this requires that the loud high frequency sound have energy or amplitude which is very great and remains pure. In actual practice, as the energy of the regurgitation increases, more and more low frequencies are produced so that the threshold of palpability is quickly reached.

The usefulness of this method of grading has been appreciated by several leading cardiologists, including Fowler[10] and Proctor Harvey.[11] This method of grading has many advantages. (1) It facilitates the teaching of grading out of 6, because Grades 3 and 4 were always the only stumbling blocks. (2) It teaches the student the relation between a thrill and a murmur, making him realize that a long thrill is never felt in the absence of a murmur. (Occasional widely split components of a loud heart sound may be palpable as a short thrill.[8]) (3) It lends itself to the grading of heart sounds.

Modern advances in auscultation make great diagnostic use of the loudness of various components of the heart sounds, e.g., the loudness of the pulmonary component of the second sound in atrial septal defect and in pulmonary hypertension, the loudness of the opening snap as a sign of mobility of the mitral valve, and the loudness of the S_3 and S_4 gallop as a sign of failure or left ventricular pressure load. Despite this, little has been written to support the grading of heart sounds in the same way as one would grade murmurs.

Yet its many advantages make one think that the reason for ignoring the grading of sounds is probably an inability to agree even on the grading of murmurs. Now that we have an easy method of grading murmurs, we can apply the same method to sounds because a palpable sound becomes Grade 4 or more, and if it is heard with the stethoscope off the chest, it becomes Grade 6, etc., the same as for murmurs.

A diagram of auscultatory findings can be used to grade sounds by filling in the required number of background blocks drawn one on top of the other, each block equaling one grade. A footnote grading chart in one corner teaches the system at a glance, even showing which grades imply palpability of either a heart sound or a murmur. These heart-sound grading blocks may now also serve as a standard of loudness for the murmurs. The murmurs are drawn as high as the grade shown by the heart-sound blocks (Fig. 2).

We believe that the shape and length of a murmur is easy to diagram, and it is well known that the exact sites of onset and termination of a murmur are absolutely essential to the understanding of the site of production of the murmur. The use of the diagram discourages still prevalent primitive descriptions, such as, "There was a systolic murmur at the apex." By having to give length, shape, and frequency to a murmur it becomes easy to teach the true meaning of a regurgitant or an ejection systolic murmur and so encourage the use of these terms. We avoid the general use of the word "pansystolic" in descriptions of regurgitant systolic murmurs for the following reasons.

Leatham[4,11,12] proposed the expression "pansystolic regurgitant" murmur to describe systolic murmurs that are due to mitral or tricuspid regurgitation, ventricular septal defects, or patent ductus. He tried to show, however, that "pansystolic" was often only a phonocardiographic term because, although some regurgitant murmurs seemed to the ear to occupy only part of systole, a good phonocardiogram would always show them to be pansystolic. This may be only a technical problem because we have seen in phonocardiograms murmurs of muscular ventricular septal

Fig. 2. See text.

defects which disappeared before the aortic second sound and many crescendo murmurs of mitral regurgitation which appeared to start only in mid systole exactly as they sounded with the stethoscope.[14] We believe, therefore, that all regurgitant murmurs are not necessarily pansystolic. It is also known that all pansystolic murmurs are not necessarily *regurgitant.* The word pansystolic has become synonymous with regurgitant in some minds. But the murmur of pulmonary stenosis may well start with the first sound and be "pansystolic" if it goes past the second aortic sound, i.e., it is pansystolic for the left ventricle. Finally, if the first or second sounds are missing, only simultaneous phonocardiograms or pulse tracings with phonocardiograms can prove that a murmur is or is not pansystolic. Therefore we think that the word "pansystolic" should be used only to describe phonocardiograms. For the student who has only a stethoscope we teach the term "regurgitant murmur," by which we mean that in shape and timing the murmur may be plateau or crescendo-decrescendo, but *that in either case it will start immediately* with the first sound and end at or slightly after the second sound on its side. It may be crescendo to the second sound on its side (and not start immediately with the first sound) or, more rarely, it may be decrescendo, starting immediately with the first sound. An important part of the regurgitant murmur complex is the effect of a long diastole, such as that produced by a premature contraction or atrial fibril-

lation The regurgitant murmur changes very little after a long diastole, and when soft is always dominantly of high frequency

It is also easy to teach the ejection murmur complex. The term ejection murmur is objected to by some because somehow Leatham's[11,12] original description of a semilunar valve ejection murmur as a mid-systolic crescendo-decrescendo murmur that ends before the second sound on its side came to be misinterpreted as merely any "diamond-shaped" murmur. When regurgitant murmurs were found often to be crescendo-decrescendo the word ejection was looked upon with suspicion. Now we can teach the ejection murmur complex because we expect the student not only to look for a crescendo-decrescendo effect, but also to note whether the murmur stops before the second sound of its side, whether there is a marked increase in amplitude after a longer diastole, or whether its onset is with an ejection click all characteristics of an ejection murmur The diagram should have a place to note the effect of a longer diastole, in order to remind the auscultator to listen for this.

The diagram can serve as a means of training the student of cardiology to acquire any habits of auscultation that the chief of a cardiology teaching service desires. For example, it is compulsory in most services to make the beginner aware of the normal and abnormal splitting of the second sound By providing a place on a graph for noting the width and movements of the split with respiration a constant reminder is provided Since in our hospital we wish to teach our students the value of listening in the neck for heart sounds, murmurs and venous hums, we merely include this on our diagram Every instructor may make his own additions to fit the needs of advances in auscultation

We agree with Segall that the writing should be done with the stethoscope in one hand and a pencil in the other This graph is for improving the ability to auscultate it is not a memory test A phonocardiogram should also be used as much as possible in training students We believe that we can tell the phonocardiogram trained auscultator from the self made one by the former's astuteness in timing and in hearing shapes, frequencies, splits and extra sounds. We believe that students cannot be adequately trained to auscultate without the help of stethophones, oscilloscopes, and tracings If no oscilloscopes or stethophones are available, then this graphic notation method is probably the best way to teach auscultation

It has been argued that fixing an actual phonocardiogram to the hospital chart is better than any written method of displaying what the patient actually has. The fallacy of this reasoning lies in the following facts (1) There are many high frequency murmurs that are difficult or impossible to show well on most phonocardiograms. (2) Some patients are too ill to be brought to a phonocardiograph machine with recording apparatus. (3) There is no accepted standard grading of amplitude or any way of showing the frequency quality site of the microphone or position of the patient on the usual phonocardiogram without extra symbols. Therefore, writing cannot be eliminated even on a phonocardiogram

In many centers good copies of phonocardiograms and various pulse tracings are on the chart in all cardiac workups. This may be an admirable goal for all hospitals, but we hope that it will become only a supplement and not a substitute for a good auscultation diagram lest we sacrifice one of the best methods of training in auscultation

We are *not* recommending the graphic method of recording auscultation as a routine for every hospital chart at present but only for the cardiac workups in offices or in hospitals with a training program in cardiology

Summary

An improved graphic method of diagramming heart sounds and murmurs is presented for the purpose of advancing training in auscultation and to facilitate speed and clarity of communication in cardiology workups. This graphic method is made possible by more recent concepts in the grading of amplitude on a scale of 6, so that a means of grading heart sounds as well as murmurs becomes practical discuss the valu of using palpabll

separate Grade 3 from Grade 4 sounds or murmurs

We have tried to show how the word pansystolic may be misleading and should be replaced by regurgitant in the description of auscultatory findings. The regurgitant and ejection murmur complexes are described and we show how a diagram may be used to teach students to learn these concepts.

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The intravenous use of ethacrynic acid in the management of acute pulmonary edema

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Ethacrynic acid (Fig. 1) has been studied for the past 3 years as a new diuretic agent.[1-3] It is an alpha beta unsaturated ketone derivative of aryloxyacetic acid. If given orally or intravenously it produces a marked increase in the flow of urine and the excretion of sodium and chloride. The excretion of potassium is only moderately increased. Ethacrynic acid seems to interfere with the reabsorption of electrolytes in the ascending loop of Henle and to a lesser degree with the reabsorption of sodium chloride in the proximal tubule. The onset of action of ethacrynic acid is prompt when given intravenously. It is effective within minutes and it reaches its maximum diuretic activity within 30 minutes. This makes it preferable to mercurial diuretics.

This study concerns the effects of a single intravenous dose of 50 mg. of ethacrynic acid given to 15 patients with acute pulmonary edema. All the patients were in chronic congestive heart failure, they were all digitalized, and they were all on various diuretic regimens. These patients were classified between III D and IV E according to the criteria of the New York Heart Association. Five of the patients had rheumatic heart disease, 6 patients had arteriosclerotic heart disease, and 4 patients had both hypertensive and arteriosclerotic heart disease. Each patient was seen in a bout of acute pulmonary edema, and the effects of intravenous ethacrynic acid, 50 mg., were recorded. Urinary volumes and the output of sodium, potassium, and chloride were measured for 1 to 2 hours after injection in consecutive 15 minute specimens. In several patients the usual methods for the treatment of pulmonary edema had already been applied prior to the use of ethacrynic acid, but little change had occurred in the severity of the symptoms. However, since the more usual methods of therapy for acute pulmonary edema had not been used in all of the patients treated, no effort to compare the therapeutic efficiency of ethacrynic acid to that of other forms of treatment will be made. Observations on the response of 2 patients to this



Fig. 1. Structural formula of ethacrynic acid [2,3-dichloro-4-(2-methylenebutyryl) phenoxy] acetic acid $C_{13}H_{12}Cl_2O_4$

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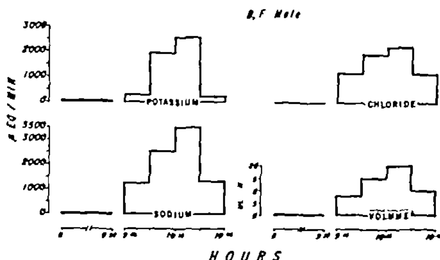


Fig 2 Case 1 Output of ur ne and excretion of elec t olytes after 50 mg of ethacry nic ac d intravenously at 15-m ut ntervals.

form of treatment will be given in detail since they are representative of the group and subsequently the findings in the entire group will be presented

C 1 The first patient wa a 66-year-old white m who had been seen 7 months previously be- use of ut pulmonary edema He had had arterio-clerotic heart disease a evidenced by nginal yndrome and myocardial infarction for t least 6 years and had had intractable c ngestive heart failure with ncreasing limitation of activity despit digitalis low-sodium diet, Mercuhydrin nd hlorthalidone W th oral ethacrynic acid there had been a moderate improvement in hi condition til he uddenly developed extreme dy pnea orthopnea nd a kle edema H w given 50 mg of Demerol int amuscularly and nasal oxygen One hour later fter no evidence of im- provement 50 mg of ethacry ic acid wa given intra enou l Fifteen min tes later the patient oided 120 of urine nd the dy pnea and orthop- nea were noted to diminish B the end of 1 hour diuresis t taled 90 c and the patient wa free of distre

Fig 2 ba graph presenting the pertinent data on urinary volume nd the excret on of elec trolytes Time is plotted along the bscissa and electrolyte excretion in microequ valent per min- ute on the ordinate A marked increase i urinary excretion of sodium is seen in the first 15 minutes The increase is even more marked in the subsequent two 15-minute peri d In the final 15-minut specimen of the first hour lectrolyt excretion is the same s in the first 15-minut period of treat ment. The excretion of hloride is also m kedly increased, and there is n increase in the excretion of pota ium. The ncrease in urinary excretion of potassium after the intravenou administration of ethacrynic acid, although quite marked is less marked than the increase in the excretion of sodium

Chloride d'uresis in this patient is not so striking as sodi m diuresis

The numerical values for these lectrolyt data are shown in T ble I

Case 2 The second patient was a 53-year-old white man who wa seen early one morning in acute pulmonary edema. The patient had had rheu- matic heart disease for more than 20 years.

In 1957 t the age of 46 he had had a mitral commissurotomy because of mitral stenosis and insufficiency with intractable heart failure which had incapacitated him f r 5 ears After the opera



Fig 3 Case 2 Chest x-ray film shows the heart compatible with mitral stenosis nd insufficiency in congestive failure.

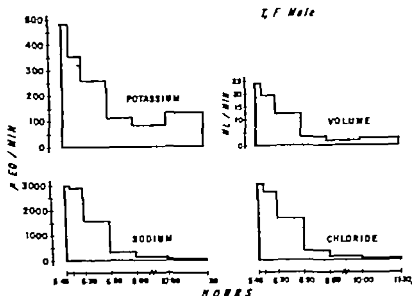


Fig. 4. Case 2. Output of urine and excretion of electrolytes after 50 mg. of ethacrynic acid intravenously at 15-minute intervals.

Table I. Data on urinary electrolytes after 50 mg. of ethacrynic acid intravenously (F.B., 66-year-old white male)

Specimen number	Volume (ml./min.)	Na (μEq/min.)	K (μEq/min.)	Cl (μEq/min.)	Clearance of uric acid
Control (90 min.)	0.7	64	59	26	9.1
1. (15 min.)	8.0	1,220	304	1,220	20.9
2. (15 min.)	14.0	2,520	1,960	1,960	8.9
3. (15 min.)	20.0	3,400	2,600	2,780	9.5
4. (15 min.)	10.0	1,270	240	1,200	6.4

tion there had been some improvement in his condition for about 6 years, but during the past year the patient had developed increasing congestive heart failure. One morning early this year the patient was awakened from sleep with acute dyspnea. Examination revealed an agitated, apprehensive man with orthopnea. The neck veins were distended and the liver was enlarged. On auscultation, coarse râles were heard over both lung fields. Fig. 3 shows x-ray film of this patient's chest taken several months prior to this episode of pulmonary edema. The patient was given 50 mg. of Demerol, and rotating tourniquets were applied to his extremities. There was no response to this treatment. After 45 minutes, 50 mg. of ethacrynic acid diluted in 20 c.c. of distilled water was given intravenously. Within 15 minutes the patient began to diurese and at the end of the first hour his urinary output totaled 1,220 c.c., with 7,500 mEq. of sodium, 1,075 mEq. of potassium, and 7,370 mEq. of chloride. The dyspnea and orthopnea decreased ½ hour after treatment, and by the end of 1 hour the patient was comfortable and free of distress.

Fig. 4 shows in graphic form the values of each 15-minute urinary specimen.

All of the 15 patients showed a prompt and good diuresis after treatment. The output of urine ranged from 180 to 1,270 ml. with an average of 522 ml. per hour. The excretion of sodium averaged 4,888 mEq. per minute. The excretion of potassium averaged 1,198 mEq. per minute. The excretion of chloride averaged 5,046 mEq. per minute. In no patient did the output of potassium exceed that of sodium or

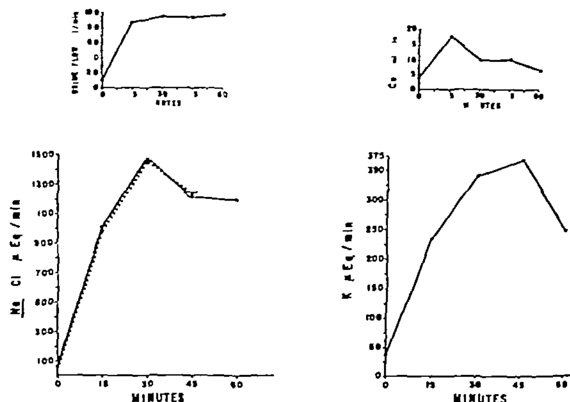


Fig. 5. Composite data on urinary electrolytes and clearance of uric acid after intravenous ethacrynic acid in 15 patients.

chloride (Fig. 5). The diuresis was rapid in onset and contributed strikingly to the lessening of the pulmonary edema in every patient except one. The single exception was a patient with mitral stenosis and advanced heart failure. There was only a mild diuresis after intravenous therapy and a temporary improvement in her condition. Despite this, the patient died 12 hours after treatment, with persistent signs of pulmonary edema.

There were no adverse reactions during intravenous administration of ethacrynic acid, except in the case of one patient in whom phlebitis was produced when the material was not properly injected into the vein.

In the upper right corner of Fig. 5 a plot of uric acid clearance is shown. In almost all cases the values at intervals of 15 and 30 minutes after intravenous ethacrynic acid are much higher than either the pretreatment value or the values observed at intervals of 45 and 60 minutes. This would suggest that ethacrynic acid may resemble chlorothiazide in its paradoxical effect on the excretion of uric acid.[4] When given in large doses intravenously, it increases the excretion of uric acid, whereas small doses may cause retention of uric acid.

In summary, the results in 15 patients with pulmonary edema who were treated with 50 mg. of ethacrynic acid intravenously are presented. Ethacrynic acid was found to be another valuable agent for the treatment of pulmonary edema. Because of its extremely rapid diuretic action, its use in severe pulmonary edema is especially recommended.

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Experimental and laboratory reports

Effect of exercise and isoproterenol on the cardiovascular dynamics in complete heart block at various heart rates

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We have previously reported the hemodynamic consequences of varying the heart rate[1-3] in patients with complete heart block. Subsequently the effect of exercise, isoproterenol[4] and digitalis[5] on these patients at one fixed heart rate was described and it was shown that the cardiac output increases during exercise, during infusion of isoproterenol, and after digitalization at the expense of an increase in stroke volume.

This study was undertaken in order to further clarify the role of the stroke volume in regulating the cardiac output during exercise in conditions in which the heart rate was maintained fixed at three rates throughout the study.

Material and methods

Six patients with complete heart block were studied. Etiology of the heart block in 3 of the patients was considered to be coronary artery disease as judged by clinical and laboratory evidence. No probable etiology could be assigned in the other 3 patients, all of whom developed heart block past the age of 50. At the time of the study the patients did not have clinical manifestations of heart failure. The average age of the patients at the time of the study was 66.5 years.

Right heart catheterization was performed under local anesthesia without premedication. A No. 6 biopolar electrode catheter† was introduced into the right antecubital vein and advanced to the apex of the right ventricle.

Cardiac output was determined by the indicator-dilution technique with indocyanine‡ (Cardiogreen) as an indicator. Details of this technique were described in our previous report.[2] The indicator was rapidly injected into the left cubital vein, and sampling was done from the right brachial artery through a No. 18 Cournand needle. A Gilford cuvette densitometer§ (Model 103 IR) was used to detect the injected dye. The curves were recorded with the Electronics for Medicine‖ (Model DR-8) oscilloscopic photographic recorder

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at a paper speed of 5 mm per second The cardiac output was calculated by the Stewart Hamilton method[7,8] in 3 patients. In the other 3 patients the output of the densitometer was coupled with a dye dilution computer* (Model 130) and the cardiac output was derived from the area calculated by the computer[9]

The output of a transistorized pacemaker† (Model TR 3) was connected to the electrode catheter placed in the right ventricle and the heart rate was controlled by this means. The current of the pacemaker unit was set at 1 8 to 3 0 milli amperes.

The pacemaker rate was set initially to a rate of 50 beats per minute and subsequently raised to 70 and 90 beats per minute. Three to five determinations of all measurements were obtained at rest and averaged The patients were then exercised in a supine position on a calibrated bicycle ergometer.‡ All patients were subjected to exercise at a workload of 206 Kg M min for a period of 4 minutes. During the exercise, measurements were taken every minute and at 2 4 and 10 minutes after exercise The patients were then allowed to rest for 15 minutes, after which the same procedure was performed at a heart rate of 70 and then at 90 beats per minute. Thirty determinations of the cardiac output and related parameters were obtained in each patient subjected to the exercise test.

Isoproterenol studies were performed in 2 patients—in one at heart rates of 50 70 and 90 per minute, and in the other at rates of 50 and 70 per minute The drug was infused intravenously at a rate of 2 μg per minute for a period of 15 minutes. Cardiac output was determined before infusion (three times) at 1 2 4 6 10 and 15 minutes during infusion and at 10 minutes after infusion of the drug was discontinued.

The ventricular rate was measured using Lead II of the electrocardiogram simultaneously recorded with the dye dilution curves. The atrial rate was measured from the P P interval of the electrocardiogram

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Arterial pressures were recorded with a P23Db Statham strain gauge. Mean pressures were obtained by electronic filtering Peripheral resistance average ventricular power and stroke power were calculated from previously described formulas.[10] Peak systolic pressure was used in Sarnoff's formula[11] to calculate the tension time index. Ejection time was calculated from the indirect carotid tracings.[12]

Results

Effect of exercise at various fixed heart rates

CARDIAC INDEX At a heart rate of 50 the resting cardiac index was abnormally low in 3 patients, and normal in the fourth patient The average resting figure for the group at the rate of 50 per minute was 2 11 L/min /M[2] In one patient (T B) the resting cardiac index rose as the heart rate increased to 70 and 90 per minute (Tables I and II) In the other 3 patients the resting cardiac index did not change significantly with an increase in rate. During exercise the cardiac index rose for all

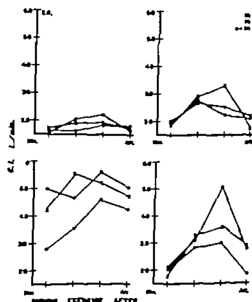


Fig 1 Effect of three periods of exercise on the cardiac Index (C.I) of 4 patients with complete heart block and with fixed ventricular rates of 50 70, and 90 beats per minute. Note an increase in the cardia Index for all three rates, with a better response obtained for the rates of 70 and 90 per minute

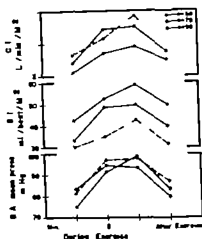


Fig. 2. Effect of exercise at three fixed rates of 50, 70, and 90 per minute on the cardiac index (C.I.), stroke index (S.I.), and brachial artery (B.A.) mean pressure. The figures represent the average for the group.

three rates, with a maximal increase observed during the fourth minute of exercise. At this time, the average cardiac index for the group was 2.93 (38 per cent), 3.51 (45 per cent) and 3.86 (45 per cent) L./min./M.² for heart rates of 50, 70, and 90 per minute, respectively (Figs. 1 and 2). This type of response was uniformly present in the 4 patients studied. The rise in the cardiac output occurred with the onset of exercise and was maintained throughout the 4-minute period of exercise.

STROKE INDEX. The average resting stroke index was 42, 34, and 30 ml./beat/M.² for the rates of 50, 70, and 90 per minute, respectively. During exercise the stroke index rose to a maximum average figure of 50 (40 per cent), 50 (47 per cent), and 43 (43 per cent) ml./beat/M.² for those rates (Figs. 2 and 3).

CENTRAL BLOOD VOLUME INDEX. This measurement was nearly identical for the resting figures obtained in 3 patients. During the fourth minute of exercise there was a slight rise in this parameter for the heart rates of 50, 70, and 90 per minute (Fig. 4).

MEAN CIRCULATION TIME. The mean circulation time averaged 25, 27, and 25 seconds for the control figures for heart rates of 50, 70, and 90 per minute. During exercise there was a minimal shortening of this measurement for the rates of 70

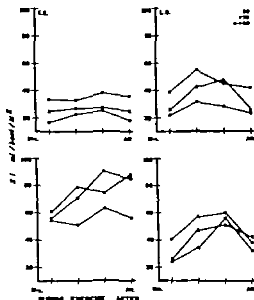


Fig. 3. Effect of three periods of exercise on the stroke index (S.I.) in 4 patients with complete heart block and with fixed ventricular rates of 50, 70, and 90 per minute. Note a rise in the stroke index for all three rates. The greater increase in the stroke index occurred for the rate of 50 per minute.

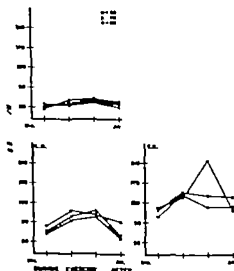


Fig. 4. Effect of exercise at three fixed ventricular rates of 50, 70, and 90 per minute on central blood volume index (C.B.V.I.) in 3 patients with complete heart block. Note an increase in this parameter during exercise for all three rates.

Table I Cardiovascular dynamics during exercise in 4 patients with complete heart block at

Patient Sex Age BSA (M²)	Event	CI (L./min./M²) 50	CI 70	CI 90	SI (ml./beat/M²) 50	SI 70	SI 90	CBVI (L./M²) 50	CBVI 70	CBVI 90	MCT (sec.) 50	MCT 70	MCT 90	BP systolic (mm. Hg) 50	BP 70	BP 90
E.C.	C	1 69	1 78	1 52	34	25	17	0 53	0 54	0 50	19	18	20	160	130	120
F 70	2m D	1 64	1 91	2 04	33	27	23	0 57	0 54	0 64	21	17	19	190	175	180
1 26	4m D	1 88	1 90	2 22	38	27	25	0 64	0 60	0 65	20	19	18	200	170	180
	After	1 81	1 76	1 63	36	25	18	0 57	0 53	0 56	18	18	21	150	140	140
L.O	C	1 95	1 85	1 97	39	26	22	0 83	0 72	0 68	26	24	21	180	140	125
M 71	2m D	2 77	2 94	2 77	55	42	31	1 11	1 00	0 93	24	21	20	185	165	160
1 70	4m D	2 27	3 30	2 53	45	47	28	1 05	1 12	1 01	29	20	24	190	190	180
	After	2 13	1 74	2 17	42	25	24	0 90	0 66	0 57	25	23	16	180	140	172
T B	C	2 80	4 25	5 00	56	61	56	—	—	—	—	—	—	75	88	75
M 68	2m D	3 54	5 53	4 67	71	79	51	—	—	—	—	—	—	100	98	80
2 14	4m D	4 60	5 24	5 66	92	75	63	—	—	—	—	—	—	100	95	85
	After	4 25	4 75	5 05	85	68	56	—	—	—	—	—	—	85	90	80
E.S	C	2 01	1 81	2 12	40	26	24	1 04	1 17	1 18	31	39	31	160	155	130
M 68	2m D	2 86	3 30	3 08	57	47	34	1 47	1 53	1 47	31	28	29	200	190	195
2 21	4m D	3 00	3 60	5 05	60	51	56	1 23	1 46	2 14	25	24	25	205	180	195
	After	1 88	2 91	2 85	38	42	32	1 24	1 42	1 16	39	29	24	145	138	135
Average	C	2 11	2 42	2 65	42	34	30	0 80	0 81	0 78	25	27	25	144	128	112
	2m D	2 70	3 42	3 14	54	49	35	0 90	1 02	1 01	25	22	23	168	157	153
	4m D	2 93	3 51	3 86	59	50	43	0 97	1 06	1 26	25	21	22	173	158	160
	After	2 51	2 79	2 92	50	40	32	0 90	0 87	0 76	27	23	20	140	127	131

Note that many other determinations were obtained during and after exercise. They were not included in this table for the purpose of
CI Cardiac index. SI Stroke index. CBVI Central blood volume index. MCT Mean circulation time. BP: Blood pressure. P.[illegible] D: During

and 90 per minute, without change for the heart rate of 90 per minute.

ARTERIAL PRESSURE. The average resting systolic pressure was 144 128 and 112 mm. Hg for the rates of 50 70 and 90 per minute This pressure rose uniformly during exercise for all three rates, being 173 158 and 160 mm. Hg for the heart rates of 50 70 and 90 per minute respectively observed during the fourth minute of exercise (Fig 2) The changes in diastolic pressure were variable however There was a tendency toward a rise during exercise in all patients for heart rates of 50 and 90 per minute. The mean pressure rose during exercise in all patients for all three heart rates. The average resting figures were 70 71 and 65 mm Hg for the rates of 50 70 and 90 beats per minute, as compared with the exercise figures of 94 99 and 98 mm. Hg for the same heart rates.

PERIPHERAL RESISTANCE. The peripheral resistance decreased uniformly during exercise in all patients for any given heart rate. The resting figures were 2,021 1 689 and 2 011 dynes sec./cm⁵ for the rates of 50 70 and 90 per minute as compared with exercise figures of 1,818, 1 665 and 1 608 dynes sec./cm⁵ obtained during the fourth minute of exercise (Fig 5)

EJECTION TIME. There was a minimal increase in the average ejection time during exercise for the rates of 70 and 90 per minute (Tables I and II) This difference however was not considered to be significant.

TENSION TIME INDEX. This parameter increased during exercise in all but one patient. The resting figures of 2,292 2 468, and 2,363 mm Hg per second were obtained for the rates of 50 70 and 90 per minute which compares with 2,918 3,347 and 3 703 mm. Hg per second obtained

fixed ventricular rates of 50 70 and 90 per minute

BP diastolic (mm. Hg)			BP mean (mm Hg)			P.Res. (dynes sec /cm)			VP (Kg.M /min /M ²)			AR (beats/min)		
50	70	90	50	70	90	50	70	90	50	70	90	50	70	90
65	95	70	90	65	100	3 380	2 310	4 166	3 23	3 14	2 47	78	76	83
75	65	80	110	100	110	4 251	3 319	3 410	4 28	4 59	5 04	—	—	—
65	75	88	100	105	115	3 375	3 500	3 285	5 13	4 43	5 49	90	90	93
60	60	85	85	85	105	2 968	3 962	4 077	3 71	3 35	3 11	88	85	83
60	65	75	95	85	85	2 288	2 158	2 029	4 82	3 52	3 34	83	88	90
75	70	70	100	95	95	1 698	1 520	1 609	7 05	6 85	6 07	—	—	—
75	65	80	96	105	105	1 989	1 494	1 948	5 93	8 63	6 26	106	125	125
60	68	85	90	85	88	1 983	2 288	1 928	5 27	3 32	5 12	90	89	92
45	55	50	60	68	63	800	598	485	2 77	4 99	4 94	80	65	71
50	58	50	63	70	65	683	472	525	4 76	7 27	4 95	—	—	—
48	56	55	63	72	68	527	513	449	6 18	6 67	6 40	93	93	90
45	55	50	55	65	60	452	511	444	4 81	5 71	5 36	71	65	—
70	70	65	90	85	80	1 617	1 691	1 364	4 40	3 83	3 74	71	73	73
78	78	90	105	105	120	1 324	1 148	1 360	7 88	8 63	8 27	—	—	—
75	75	85	115	115	105	1 344	1 156	752	8 48	8 90	13 56	107	125	88
65	75	70	90	100	95	1 726	1 240	1 205	3 72	3 48	3 23	73	73	70
70	71	65	83	75	82	2 021	1 689	2 011	3 85	3 97	3 62	78	75	79
71	67	72	95	92	97	1 989	1 614	1 726	5 92	6 77	5 93	—	—	—
65	67	77	94	99	98	1 818	1 665	1 608	6 27	7 08	7 74	99	108	99
57	64	72	80	83	87	1 789	1 775	1 913	4 45	4 63	4 45	81	78	81

stimulation.
Peripheral resistance VP: Ventricular power AR Atrial rate. F Female M Male BSA Body surface area C Control. or Min-

during the fourth minute of exercise (Fig 6)

VENTRICULAR POWER. The ventricular power rose significantly during exercise in all patients for all three heart rates. The resting figures were 3 85 3 97 and 3 62 Kg M /min./M ² for rates of 50 70 and 90 per minute. The maximum figures during exercise were 6 27 7 08 and 7 74 Kg M./min /M ² for the same rates (Fig 7)

STROKE POWER. The stroke power at rest was normal being 239 194 and 161 Gm M /sec./M ² for the rates of 50 70 and 90 per minute respectively During exercise there was a uniform rise in this parameter to an average of 414 332 and 333 Gm M /sec./M ² for the rates of 50 70 and 90 per minute for the fourth minute of exercise (Fig 8)

ATRIAL RATE. The resting atrial rate averaged 78 99 and 81 per minute for ventricular rates of 50 70 and 90 per minute and during exercise the atrial rate rose to an average maximum of 99 108 and 99 per minute (Tables I and II)

Effect of isoproterenol at various fixed heart rates

CARDIAC INDEX. In one patient (N B) the cardiac index at rest was 2.28 2 47 and 3 01 L./min M for the rates of 50 70 and 90 per minute. During infusion of isoproterenol the cardiac index rose for all three rates (Table III) The rise in this parameter began within 1 minute after the beginning of infusion and reached a maximal response at the sixth minute of infusion (Fig 9) The maximal increase in the cardiac index occurred for the heart rate of 90 per minute when the cardiac index was 3 70 L./min./M as compared with 3 74 and 3 13 L./min., M for the heart rates of 50 and 70 respectively In the second patient (E.G) the response to isoproterenol was qualitatively similar to

Table II Cardiovascular response to exercise at three fixed ventricular rates of 50 70 and 90

Patient	HR	CI (L./min/M²)			SI (ml./beat/M²)			BP mean (mm Hg)		
		Rest	Exer	% Chg	Rest	Exer	% Chg	Rest	Exer	% Chg
E.C.	50	1 69	1 88	11	34	38	12	90	100	11
	70	1 78	1 90	6	25	27	8	65	105	61
	90	1 52	2 22	46	17	25	47	100	115	15
L O	50	1 95	2 27	16	39	45	15	95	96	1
	70	1 85	3 30	78	26	47	80	85	105	23
	90	1 97	2 53	28	22	28	27	85	105	23
T B	50	2 80	4 60	64	56	92	64	60	65	8
	70	4 25	5 24	23	61	75	22	68	72	5
	90	5 00	5 66	13	56	63	12	65	68	4
E.S	50	2 01	3 00	49	40	60	50	90	115	27
	70	1 81	3 60	98	26	51	96	85	115	35
	90	2 12	5 05	138	24	56	133	80	105	31
Average	50	2 11	2 93	38	42	59	40	83	94	13
	70	2 42	3 51	45	34	50	47	75	99	32
	90	2 65	3 86	45	30	43	43	82	98	19

Note that the exercise figures were obtained during the fourth minute of exercise.
HR Heart rate. *Exer* Exercise. *% Chg* Per cent change. For key to other abbreviations see footnote to Table I

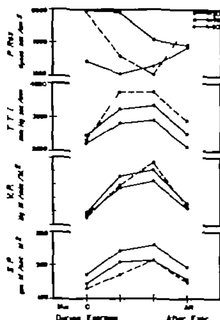


Fig 5 Effect of exercise at three fixed ventricular rates of 50 70 and 90 per minute on the peripheral resistance (*P Res*), tension time index (*T.T.I.*), average ventricular power (*V.P.*) and stroke power (*S.P.*). The figures represent the average for the group.

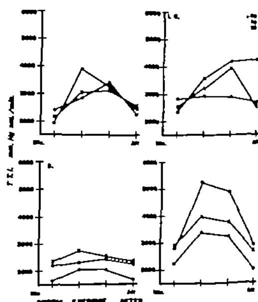


Fig 6 Effect of exercise at the three fixed ventricular rates of 50 70 and 90 per minute on the tension time index (*T.T.I.*) in 4 patient with complete heart block. Note an increase in the parameter for all three rates.

per minute

P.Res. (dynes sec./cm.)			V.P. (Kg.M./min./M²)			A.R. (beats/min.)		
Rest	*Exer*	*% Chg*	*Rest*	*Exer*	*% Chg*	*Rest*	*Exer*	*% Chg*
3 380	3 375	1	3 23	5 18	60	78	90	15
2 310	3 500	51	3 14	4 43	41	76	90	18
4 166	3 285	22	2 47	5 49	122	83	93	12
2 288	1 989	14	4 82	5 93	23	83	106	27
2 158	1 494	31	3 52	8 63	145	88	125	42
2 029	1 948	4	3 34	6 26	87	90	125	38
800	527	35	2 77	6 18	123	80	93	16
598	513	15	4 99	6 67	33	65	93	43
485	449	8	4 94	6 40	29	71	90	26
1 617	1 384	15	4 40	8 48	92	71	107	50
1 691	1 156	32	3 83	8 90	132	73	125	71
1 364	752	45	3 74	13 56	262	73	88	20
2 031	1 818	11	3 85	6 27	62	78	99	26
1 689	1 665	2	3 97	7 08	78	75	108	44
2 011	1 608	21	3 62	7 74	113	79	99	25

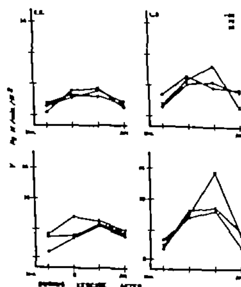


Fig. 7. Effect of exercise at three fixed ventricular rates of 50, 70 and 90 per minute on the average ventricular power (V.P.) of 4 patients with complete heart block. Note an increase in this parameter for all three rates.

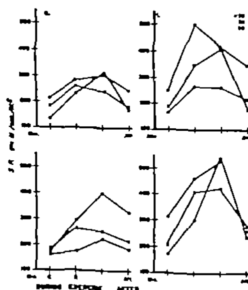


Fig. 8. Effect of exercise at three fixed ventricular rates of 50, 70 and 90 per minute on the stroke power (S.P.) in 4 patients with complete heart block. Note an increase in this parameter for all three rates.

Table III Effect of intravenous infusion of 2 μg per minute of isoproterenol on the cardiac dy-

Patient Sex Age BSA (M^2)	Event	CI ($L/min/M^2$)			SI ($ml/beat/M^2$)			BP systolic (mm Hg)			BP diastolic (mm Hg)			BP mean (mm Hg)		
		50	70	90	50	70	90	50	70	90	50	70	90	50	70	90
N B	C	2 28	2 47	3 01	46	35	34	175	175	180	60	55	65	90	100	100
F 68	2m D	3 91	3 33	3 51	78	48	39	170	175	180	35	30	50	65	60	80
1 78	6m D	4 09	3 48	3 78	82	50	42	185	190	180	30	30	45	70	65	75
	10m D	3 20	3 03	3 43	64	43	38	185	190	170	40	40	40	90	60	65
	15m D	3 24	3 13	3 70	65	45	41	180	175	180	50	30	35	90	70	70
	After	2 27	2 28	2 40	45	33	27	175	170	180	45	55	65	85	90	95
E G	C	2 14	2 62	—	43	37	—	170	145	—	40	42	—	75	78	—
M 72	2m D	2 53	3 57	—	50	51	—	165	150	—	40	30	—	72	65	—
2 12	6m D	3 33	3 40	—	67	49	—	165	145	—	35	35	—	60	75	—
	10m D	3 72	3 92	—	75	56	—	175	145	—	35	35	—	65	60	—
	15m D	4 44	3 92	—	69	56	—	170	145	—	30	35	—	65	60	—
	After	2 28	2 83	—	46	41	—	170	160	—	40	48	—	80	80	—

Note that many other determinations were obtained but were not included in this table for the purpose of simplification.
ET Ejection time *TTI* Tension time index *SP* Stroke power For key other abbreviations see footnot T ble I

that in Patient N B with the exception that maximal effect was obtained at 10 minutes during infusion of the drug

STROKE INDEX The stroke index rose during infusion of isoproterenol in both patients. The maximal response was obtained for the heart rate of 50 with lesser degrees of rise for the rates of 70 and 90

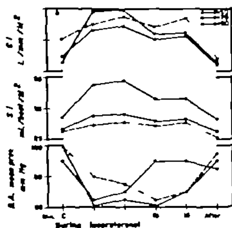


Fig 9 Effect of 2 μg of isoproterenol at three fixed ventricular rates on the cardiac index (*CI*) stroke index (*SI*), and brachial artery (*BA*) mean pressure in one patient with complete heart block. Note an increase in the cardiac index and stroke index for all three rates. The increase in the stroke index was proportional to the heart rate

per minute The resting figures for one patient were 46 35 and 34 ml/beat/M^2 for the heart rates of 50 70 and 90 per minute respectively (Fig 9) During infusion of isoproterenol the stroke index rose to 65 (41 per cent) 45 (28 per cent) and 41 (20 per cent) ml./beat/M^2 for these rates The figures obtained for the second patient also followed the same trend

SYSTEMIC PRESSURES The systolic pressure rose slightly during infusion of isoproterenol for the rates of 50 and 70 per minute in one patient, but there were no significant changes in the second patient There was a uniform decrease in the mean and in the diastolic pressures for all three rates (Fig 9) The pulse pressure therefore increased in both patients for all three rates.

PERIPHERAL RESISTANCE There was a marked decrease in peripheral resistance during infusion of this drug for all three rates in both patients studied The resting figures in one patient were 1 773 1 810 and 1 489 dynes sec./cm^5 as compared with 1 246 1 003 and 849 dynes sec./cm^5 during the fifteenth minute of infusion of the drug for heart rates of 50 70 and 90 per minute respectively (Fig 10) The same type of response was obtained

namics at various fixed ventricular rates

	P.Res (dynes sec./cm)	ET (sec.)			TTI (mm. Hg sec./min.)			VP (Kg M /min./M)			SP (Gm M / sec./M ²)		
	90	50	70	90	50	70	90	50	70	90	50	70	90
9	1 489	0 35	0 28	0 30	1 062	3 430	4 860	5 47	5 93	7 44	313	303	276
8	1 014	0 26	0 32	0 29	2 210	3 920	4 698	9 12	8 00	8 68	703	337	333
8	889	0 29	0 32	0 27	2 652	4 256	4 374	10 40	9 10	9 35	717	406	385
87	849	0 30	0 31	0 27	2 775	4 123	4 131	8 14	7 92	8 00	543	365	329
03	849	0 28	0 31	0 28	2 520	3 797	4 336	8 01	7 52	9 15	572	347	363
69	1 773	0 34	0 31	0 30	2 975	3 689	4 860	5 45	5 31	5 93	321	245	220
21	——	0 30	0 25	——	2 550	2 537	——	4 99	5 19	——	333	296	——
96	——	0 29	0 26	——	2 391	2 730	——	5 72	7 31	——	394	401	——
52	——	0 29	0 23	——	2 392	2 537	——	7 53	6 73	——	519	384	——
76	——	0 29	0 27	——	2 537	2 740	——	8 94	7 76	——	616	410	——
11	——	0 28	0 28	——	1 380	2 380	——	8 02	8 02	——	572	572	——
1	——	0 31	0 29	——	635	3 248	——	5 32	6 20	——	343	305	——

d patient for heart rates of r minute.

TIME. There was a slight de ejection time obtained during oproterenol for all three rates t and no significant changes patient.

TENSION TIME INDEX. The tension time index decreased for the rates of 50 and 90 without significant changes for the rate of 70 per minute during infusion of the drug (Fig. 10).

VENTRICULAR POWER AND STROKE POWER. There was a uniform rise in both parameters during infusion of isoproterenol for all ranges of rate in both patients studied (Fig. 10).

Discussion

Previous hemodynamic observations have shown [illegible] that the cardiac output in patients with complete heart block can be increased proportionally to the rate of artificial pacing up to a point at which a maximal response is obtained. Further increase in rate results in a decline in the cardiac output. We have found that this "optimum response" occurs at a rate between 70 and 80 beats per minute (average 72 beats per minute) with a few patients having a maximal response around 90 per minute. In addition it was shown that exercise and infusion of isoproterenol at the level of optimum fixed rate of pacing results in a significant rise in the cardiac output, which occurs as a result of an exclusive increase in the stroke volume.[4] The present study indicates that for any given fixed ventricular rate the cardiac output and the stroke volume rise during exercise and during infusion of isoproterenol to an almost identical level with the best response obtained at rates of 70 and 90 per minute. The rate of rise in the stroke volume during exercise and infusion of isoproterenol is related to the heart rate with the greatest response observed for the slow rate of 50 per minute as compared with the faster rates of 70 and 90 per minute.

This observation therefore further emphasizes the important contribution of the stroke volume in regulating the cardiac output in the absence of any change in the ventricular rate.

There is little information in the literature showing the effect of exercise on the cardiac dynamics at various fixed heart rates in man. Haupt and associates and Bevegard[illegible] reported a study in 2 patients at two fixed heart rates with a single determination of the cardiac output during

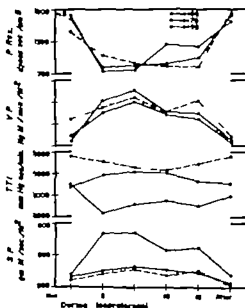


Fig. 10. Effect of 2 μg of isoproterenol at three fixed ventricular rates of 50, 70, and 90 per minute on the peripheral resistance (P. Res.), average ventricular power (V. P.), tension time index (T.T.I.), and stroke power (S.P.) in one patient with complete heart block.

exercise, and they found that the maximal increase in this parameter occurred at a faster heart rate, with a proportional decrease in the stroke volume.

On the basis of previous observations[4] it was expected that the maximal increase in the cardiac output and the stroke volume during exercise should occur at the level of the "optimum rate" of pacing, i.e., between 70 and 90 per minute. Indeed, this type of response was seen in the majority of patients studied, with a greater increase in the cardiac output occurring at a rate of 90 per minute.

Studies by Rushmer[2] and by Shepherd, Wang, and Marshall[22] in dogs with sinus mechanism have shown that the contribution of the stroke volume to the increase in cardiac output during exercise is almost exclusively related to the increase in the heart rate, with little or no change in the stroke volume. However, Warner and Toronto[23] demonstrated that exercise in dogs with heart block resulted in a rise in cardiac output and stroke volume independently of changes in heart rate. Our data confirm Warner and Toronto's observations and emphasize the important contribution of stroke volume to the increase in cardiac output during exercise in man in a condition in which the heart rate cannot be increased. Furthermore, our observations indicate that the increase in stroke volume during exercise at a fixed ventricular rate is "rate dependent," i.e., at a slow rate of 50 there are greater increases in stroke volume during exercise as compared with the increase obtained at a fixed rate of 90 per minute.

Therefore, it becomes apparent that the heart has several important control mechanisms, and the heart rate is only one of them. The important contribution of stroke volume to the increase in cardiac output cannot be neglected.

Summary and conclusions

1. The effect of exercise on the cardiac functions was studied in 4 patients with complete heart block. Exercise studies were performed at a fixed ventricular rate of 50, 70, and 90 per minute at a constant workload of 206 Kg M/min. for 4 minutes.

2. The maximal increase in the cardiac output was obtained for the rates of 70 and 90 per minute, at which time there was also an increase in stroke volume, systemic pressure, tension time index, ventricular power, and stroke power, with a decrease in peripheral resistance.

3. The results indicate that the cardiac output and the stroke volume rise during exercise to a significant degree in the absence of any change in the ventricular rate. Furthermore, the rise in the stroke volume during exercise is proportional to the heart rate, with the maximal increase in this parameter obtained for the heart rate of 50 per minute.

4. Infusion of isoproterenol at various fixed rates reproduced some of the responses obtained during exercise. The cardiac output and the stroke volume rose during administration of the drug. The maximal rise in these parameters was obtained for the rates of 70 and 90 per minute.

5. It is concluded, therefore, that the stroke volume and the peripheral resistance are powerful regulatory mechanisms of the cardiac output in conditions in which the heart rate cannot be increased. Furthermore, a better hemodynamic result

is provided by higher rates than by slower rates of pacing.

We wish to thank Miss Marilyn Hanna, Mrs. Mary Vessel, Miss Shirley Cardwell, and Miss Ann Wall for their technical assistance.

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Postmortem angiographic studies on the coronary arterial circulation

Intercoronary arterial anastomoses in adult human hearts

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There are two opposing views on the existence of large intercoronary anastomoses in normal human hearts: one is that such anastomoses, as a rule, exist, and the other is that they are absent in the majority of cases.[1]

The study reported here favors the first view, although confirming much of the evidence on which the second rests. It suggests that pertinent data obtained by workers on opposite sides of the controversy can be mutually comprehensible. It confirms the old observation that in occlusive coronary artery disease anastomoses, in time, increase in number and size between the occluded vessel and the rest of the coronary tree.

Materials and methods

Four hundred and seventy adult human hearts from patients 13 years to 96 years of age were studied by postmortem coronary arteriography. The bulk of this material has been described previously.[2-4]

The hearts were divided into two groups: in Group A, the coronary arteries were injected without prior ligation; in Group B some of these vessels were ligated before injection. These groups are characterized by sex and age in Table I. The manner in which they were processed are detailed below.

Group A. No coronary ligations (430 hearts). Four hundred and thirty hearts were examined by a modification[2-4] of Schlesinger's coronary injection plus dissection method.[6] The left and right coronary arteries were injected simultaneously through their respective coronary ostia with barium sulfate–gelatin.[7] The heart was then unrolled;[8] plain or stereoscopic angiograms of the unrolled heart were prepared, and the coronary arteries were dissected with the angiograms as guides. The ventricles were sliced in coronal fashion, and a set of stereoscopic angiograms of the slices was prepared. A tracing of the coronary arterial tree and the unrolled heart was attached to the appropriate angiogram. On this tracing, the distribution of the colored injection masses, the nature, location, and extent of coronary and myocardial lesions, and the sites of tissue blocks removed for

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Table I. Age and sex distribution of Groups A and B

Age (yr.)	Group A		Group B	
	Males	Females	Males	Females
< 20		1	0	0
20–39	8		0	2
40–59	44	38	6	6
60–79	153	93	16	6
80 on	31	53	0	4
Total	238	192	22	18

microscopy were all indicated in order to facilitate study of topographic relationships. On tracings of the ventricular slices, maps of myocardial lesions as these appeared on the cut surfaces, were outlined. Histologic sections of entire ventricular slices were prepared in selected cases.

A pneumatic apparatus with provisions for controlling the pressure was used for injection. The injection pressure—equal for both coronary arteries—was gradually raised to 200 mm. Hg and was maintained at that level for 5 minutes, then the injection was stopped. The mass used can penetrate regularly to arterioles 40 micra in diameter and inconstantly to smaller arterioles but does not enter capillaries.* Dyes of different colors mixed with the injection mass destined for each of the two coronary arteries allowed positive identification of the source of mass contained in dissected vessels. For roentgenography the specimen was laid out on fine-grain film and photographed with these values: 14 Ma., 50 kv., 10 seconds, 40 inches tube to film, and 5 degrees stereo-angle.

All hearts were classified according to the maximum degree of stenosis found in any of the major coronary arteries or their large branches (the number, length, or location of the involved segments are here excluded from analysis). Class 0 included hearts without coronary narrowing; + those with up to 25 per cent reduction in the diameter of a vessel lumen; ++ those with any reduction of 26 to 50 per cent; +++ those with any reduction of over 50 per cent; Occl., those with at least one occlusive coronary lesion.

Group B. Ligation experiments (40 hearts). Selected coronary arteries in 40 hearts were artificially occluded prior to injection. Schlesinger[4] alludes to a similar technique in an early paper.

In 20 hearts a primary branch of each of the three main coronary arteries (left anterior descending, left circumflex, and right coronary arteries) was transected between ligatures, and the injection was made proximal to the points of ligature into the left and right coronary ostia (Fig. 1). In another 20 hearts, the three main coronary arteries themselves were each transected between ligatures and then the proximal segments of all three were separately cannulated and simultaneously injected (Fig. 2). The procedure for the study and classification of these specimens was otherwise the same as that for Group A.

Detection of anastomoses. Two methods were employed to detect intercoronary anastomoses in both groups of hearts.

1. SCHLESINGER'S METHOD. Schlesinger's criteria for anastomoses[4,14] were applied, i.e., anastomoses at least 40 micra in diameter were considered to be present in hearts in which at least one of the following conditions was fulfilled: (a) a macroscopic vessel(s) intercommunicatory between two or more coronary arteries was dissected, or (b) mass introduced into one coronary artery was found in the territory of another, or (c) mass appeared distal to a coronary obstruction (occlusion or ligation

*In preliminary experiments, vascular injections [illegible] from [illegible] of [illegible] used to be [illegible] in heart [illegible] injected [illegible] with Schlesinger's barium sulfate gelatin mass.



Fig. 1. Angiogram of unrolled normal heart of Group B. Cannulas are in place in the coronary ostia. The right coronary artery was transected in the unrolling procedure, and a cut end of this vessel appears close to the right border of the photo. A branch of each of the three major coronary arteries was ligated prior to injection at the points indicated (*lines*). Retrograde flow of mass occurred distal to each of the ligated segments (*arrows*). Anastomotic routes are not clearly seen because of rich retrograde injection.

2. ANGIOGRAPHIC SURVEY. Coronary angiograms were subjected to a detailed survey. Macroscopic anastomoses were identified with a stereo-viewer and the size of their lumens were determined with a measuring magnifier (calibration 0.1 mm.; magnification ×7). During the survey it was kept in mind that, with or without stereoscopy, overlapping vessels can present a false appearance of intercommunications. For this reason, the survey avoided parts of the unrolled and sliced heart in which there was considerable overlap of vessels; only those anastomoses whose nature could not be questioned were noted, and it must be assumed that most of the gross anastomoses actually present in the specimen escaped detection.

Observations

Incidence. The number of hearts in which anastomoses were noted varied according to the presence or absence of coronary obstructions, and the method used to prove the existence of anastomoses; whether the obstruction was pathologic or artificial made no difference in this matter (Table II).

By Schlesinger's criteria, anastomoses were present in almost all hearts with coronary occlusion or ligation and absent in most of the other hearts comprising the bulk of this series. In each of the hearts with occlusion or ligation (Groups A and B), the evidence for anastomoses included retrograde injection into one or more of the obstructed vessels. Few of the anastomoses were dissectable. Those which were occurred

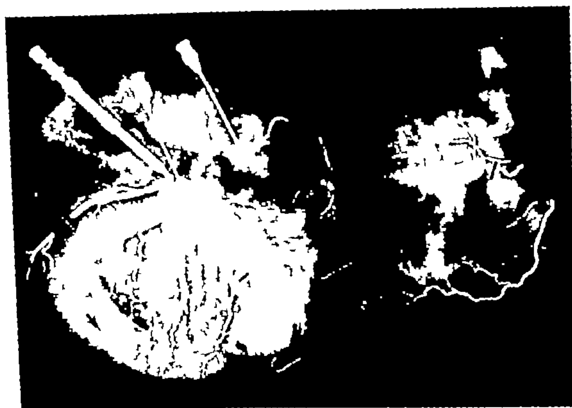


Fig. 2. Angiogram of unrolled, hypertrophic heart of Group B with a left preponderant coronary pattern.[11] Weight, 660 grams. Coronary arteries are normal. Cannulas are in place in the proximal ends of the left anterior descending, left circumflex, and right coronary arteries. Each of these major divisions of the coronary tree was ligated before injection (*lower*). Retrograde flow of mass distal to the ligation occurred in the left anterior descending and the left circumflex coronary arteries, but not in the poorly developed right coronary artery. Distal segment of the left circumflex coronary artery filled in part from the left anterior descending coronary artery via primary anastomoses in the interventricular septum and in part via secondary anastomoses connecting two branches of the left circumflex coronary artery in the free wall of the left ventricle (*arrows*). Distal segment of the left anterior descending artery filled from the proximal segment of the same vessel via septal anastomoses (*long arrow*).

Table II. Incidence of intercoronary arterial anastomoses in relation to coronary ligation, pathologic coronary occlusion, and method used for detection of anastomoses

Group of hearts	Pathologic coronary occlusion	Number of hearts	Hearts with anastomoses	
			Schlesinger's method	Angiography
Group A (430 hearts, no coronary ligation)	Absent	327	38 (12%)	132 (40%)
	Present	103	102 (99%)	103 (100%)
Group B (40 hearts, coronary ligation)	Absent	33	33 (100%)	33 (100%)
	Present	7	7 (100%)	7 (100%)

Table III Incidence of intercoronary arterial anastomoses as shown by Schlesinger's method and by angiography in hearts without coronary ligation or pathologic coronary occlusion Relation to conditions of cardiac hypoxia

Classification	*Cardiomegaly valve deformity cor pulmonale and anemia*		*Cardiomegaly (no valve deformity)*	*Valve deformity (with or without cardiomegaly)*	*Anemia*	*Cor pulmonale*
	Absent	*Present (singly or combined)*				
+++						
Number of cases	17	67	40	14	12	1
With anastomoses (M J S)*	2 (12%)	12 (18%)	6 (15%)	4 (29%)	2 (17%)	0 (0%)
With anastomoses (angio.)†	7 (41%)	31 (46%)	19 (48%)	7 (50%)	5 (42%)	0 (0%)
++						
Number of cases	24	89	51	19	11	2
With anastomoses (M J.S.)	3 (13%)	8 (9%)	6 (12%)	1 (5%)	1 (9%)	0 (0%)
With anastomoses (angio.)	8 (33%)	32 (36%)	19 (37%)	7 (37%)	3 (27%)	0 (0%)
+						
Number of cases	12	42	30	3	7	0
With anastomoses (M J.S.)	0 (0%)	5 (12%)	4 (13%)	0 (0%)	1 (14%)	0
With anastomoses (angio.)	4 (33%)	18 (43%)	13 (43%)	0 (0%)	3 (43%)	0
None						
Number of cases	20	56	21	7	18	4
With anastomoses (M J.S.)	2 (10%)	6 (11%)	1 (5%)	0 (0%)	4 (22%)	0 (0%)
With anastomoses (angio.)	9 (45%)	23 (41%)	8 (38%)	3 (43%)	6 (33%)	1 (25%)
0 to +++						
Number of cases	73	254	142	43	48	4
With anastomoses (M J S.)	7 (10%)	31 (12%)	17 (12%)	5 (12%)	8 (17%)	0 (0%)
With anastomoses (angio.)	28 (38%)	104 (41%)	59 (42%)	17 (40%)	17 (35%)	1 (25%)

*Schlesinger method.
†Angiography

in association with healed occlusions or severe coronary narrowing

By angiography anastomoses were detected in all hearts with coronary occlusions or ligations, and in many hearts which met none of Schlesinger's criteria. In some of the nonligated specimens (Group A) anastomoses shown to be present by Schlesinger's method could not be identified in the angiogram

Table III shows the lack of correlation between the incidence of anastomoses and various conditions of cardiac hypoxia other than occlusive coronary artery disease. Singly or in combination coronary narrowing cardiomegaly valve deformity cor pulmonale or anemia did not significantly increase the proportion of hearts shown to have anastomoses by either Schlesinger's method or angiography Cardiomegaly here refers to heart weights of 350 grams or more—a definition adopted from Zoll and co-workers[18] and anemia refers to a hematocrit level of 35 per cent or less, or a hemoglobin not exceeding 10 Gm —unexplained by recent episode of bleeding or by surgery The valvular deformities represented in the hearts of Group A without occlusions included a large number of aortic stenoses (29 cases) and mitral stenoses (12 cases)

The demonstrated incidence of anastomoses did not vary with the anatomic distribution of the coronary arteries,[11] or the subjects sex or age

Anatomy Intercoronary arterial anastomoses in hearts without occlusive coronary

Table IV. Incidence of retrograde injection (R.I.) in ligated vessels of Group B. Relation to coronary artery disease

Classification	Hearts (number)	Ligated main coronary arteries		Ligated branches		Ligated vessels	
		Number	With R.I.	Number	With R.I.	Number	With R.I.
Occl.	7	9	9 (100%)	12	12 (100%)	21	21 (100%)
+++	3	3	3 (100%)	6	3 (50%)	9	6 (67%)
++	10	9	9 (100%)	21	17 (81%)	30	26 (87%)
+	9	24	21 (85%)	3	3 (100%)	27	24 (87)
None	11	15	15 (100%)	18	16 (88%)	33	31 (94%)
Total	40	60	57 (95%)	60	51 (85%)	120	108 (90%)

*Table V. Comparative data on incidence of retrograde injection (R.I.) in vascular territories distal to ligations (33 hearts—Group B) and recent and old occlusive coronary lesions (103 hearts—Group A) in coronary main stems and branches**

Site of coronary obstruction	Healed occlusions		Recent occlusions		Ligations	
	R.I. present	R.I. absent	R.I. present	R.I. absent	R.I. present	R.I. absent
Main stems	121	0	27	0	45	4 (8%)
Cor. branches	64	0	8	2 (20%)	39	9 (19%)
Total	185	0	35	2 (5%)	84	13 (13%)

*Data excludes recent occlusions affecting old ones, and ligations and occlusions occurring in the same heart.

artery disease differed anatomically from those in hearts with such disease. This difference was perceived in the frequency and extent of retrograde (anastomotic) injection distal to coronary ligations and occlusions, and in the angiographic appearance of the anastomoses themselves.

Retrograde injection distal to coronary obstructions. Retrograde injection was demonstrated distal to all healed occlusions, but was not in evidence distal to a few of the recent occlusions, and some of the ligations (Tables IV and V). Most of the obstructed vessels free of mass were coronary branches. There was no correlation between the frequency of retrograde injection into ligated vessels and the severity of stenosing coronary artery disease (Table IV). Cardiomegaly did not demonstrably increase the frequency of retrograde injection into obstructed vessels. There were twelve ligated vessels into which anastomotic flow of mass did not occur. These belonged to 10 hearts, 7 of which weighed over 350 grams, 6 over 400 grams, and 4 over 550 grams.

The extent of retrograde injection beyond ligated coronary segments was not demonstrably greater in the presence of cardiomegaly (Fig. 2) or severe coronary narrowing (Fig. 8).

Angiography of anastomoses in hearts without pathologic occlusions. Among hearts without pathologic coronary occlusions 407 separate anastomoses were detected angiographically in 133 specimens of Group A (no ligations) and 142 in 33 specimens of Group B (with ligations). In the latter group of hearts, 120 of the anastomoses served to convey mass into 47 ligated vessels the pathways by which mass gained



Fig 3 Part of angiogram of unrolled normal heart of Group B Distribution of left circumflex coronary artery ligated at level indicated by the line, is shown Via secondary type of anastomoses, mass from a proximal branch of the left circumflex coronary artery entered the excluded distal segment at multiple points (*arrows*) Positive print ×1

entry into 40 other such vessels could not be traced and another 12 ligated vessels contained no mass at all. Associated conditions of relative cardiac anoxia (other than occlusive coronary artery disease) did not demonstrably alter the number of anastomoses identified as such in the angiograms. The search for anastomoses was easy where the mass occupied only a fraction of the vascular territory (Figs. 2 3 4 7 8) and difficult or impossible in areas in which direct or retrograde injection of the coronary arteries was complete or almost so (Figs. 1 and 5)

Figs. 1 to 8 illustrate the angiographic appearance of anastomoses in hearts without pathologic coronary occlusions. The course which these anastomoses followed was more often direct than tortuous. Most of them were embedded in myocardium and to dissect them out in toto was impractical in all but a few instances. Although some of the anastomoses (in Group *B*) were not fully distended with mass, those which are included in the tally were large enough to see with the naked eye. The majority of the anastomoses had calibers between 0 1 and 0 2 mm with a range of 0 05 to 0 3 mm It was not always possible to ascertain at what point the regular vessel became an anastomotic one. The longest of the anastomoses appeared to be about 4 0 cm in length (Fig 4) Anastomotic channels embedded in trabeculae carneae showed a notable tendency to follow a protracted course (Fig 4)

Table VI Sites and interconnections of primary and secondary anastomoses in 166 hearts without occlusive coronary artery disease (Group A—133 Group B—33)

Site in heart	*Primary anastomoses*				*Secondary anastomoses*				*Grand total*
	LD to RC	*LD t LC*	*LC to RC*	*Total*	*Total*	*LD to LD*	*LC to LC*	*RC to RC*	
LV	5	21	5	31	57	33	23	1	88
IVS	170	11	—	181	25	2	—	23	206
RV	82	—	1	83	36	7	—	29	119
LA	—	—	24	24	41	—	38	3	65
RA	—	—	29	29	42	—	1	41	71
Total	257	32	59	348	201	42	62	97	549

LD Left anterior descending coronary artery *RC* Right coronary artery *LC* Left circumflex coronary artery *LV* Left ventricle *IVS* Interventricular septum, *RV* Right ventricle *LA* Left atrium *RA* Right atrium.

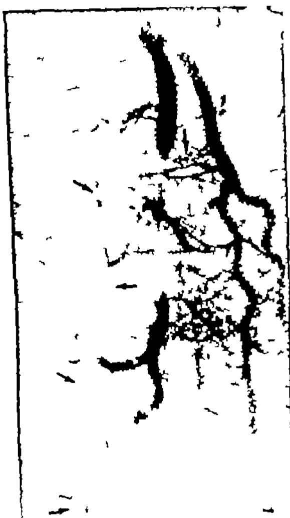


Fig. 4. Part of angiogram of unrolled hypertrophic heart of Group B showing ligated branch of left circumflex coronary artery. Distal segment received mass from proximal segment via long anastomotic channel (arrows) in trabeculae carneae. There was slight narrowing elsewhere in the coronary arterial tree. Positive print ×2.

Within the narrow range of our determinations of caliber, anastomoses tended to be larger in the presence of severe coronary narrowing (+++) or marked cardiac hypertrophy, but no appreciable difference in caliber was noted between anastomoses in small hearts without coronary narrowing and those in hearts of comparable weight with slight (+) or moderate (++) narrowing.

On the basis of their interconnections, the anastomoses could be grouped thus: (1) those between major divisions of the coronary tree (i.e., the left anterior descending, left circumflex, and right coronary arteries), (2) those which joined one branch to another within the same division, and (3) those which connected different segments of the same branch. These categories or types of anastomoses are, for convenience, here referred to as primary, secondary, and tertiary anastomoses, respectively. Examples of primary anastomoses are shown in Figs. 4, 6, 7, and 8; secondary anastomoses are illustrated in Figs. 2 and 3; and tertiary anastomoses are shown in Fig. 4.

Table VI lists the anastomoses noted in the angiograms, according to their location in the heart and the pairs of vessels they conjoined. Two thirds of the anastomoses were primary, a third were secondary, and a very few were tertiary. The most common type of anastomoses found was primary, between the left anterior descending and the right coronary arteries (Figs. 6, 7, and 8). Anastomoses of this kind were detected more often in the interventricular septum than in the anterior wall of the right ventricle (Table VI). Anastomoses in the atria comprised one third of the total number observed and often represented connections between the sinoatrial artery (ramus ostii cavae superioris—Gross) and other atrial arteries (Fig. 6). Fewer anastomoses were identified in the left ventricle than in the right ventricle or the atria, almost certainly because of the greater difficulty involved in tracing individual anastomoses in the richly arterialized regions of the former.

Angiographic appearance of anastomoses in hearts with occlusive coronary lesions. In hearts with occlusive coronary artery disease, only some of the anastomoses noted served as routes for the entry of mass into occluded vessels; the rest of the anastomoses joined pairs of coronary arteries which were patent and had been injected directly. The latter group of anastomoses did not differ in any obvious way from those described in the preceding section and need not be dealt with further here.

Anastomoses which bypassed healed occlusive coronary lesions were generally numerous and large (Fig. 10). The largest of

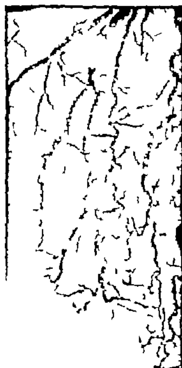


Fig. 5. Part of angiogram of unrolled heart of Group B with normal coronary arteries and a weight of 450 grams. Filling defect in large vessel near top of photo indicates level of ligation of left circumflex coronary artery. Individual anastomotic channels could not be readily identified because of rich retrograde filling of excluded vascular territory. Positive print ×1.

them was 5.0 mm. in caliber (Fig. 11). They were concentrated in the borders between the occluded vessels and the rest of the coronary tree. They included primary, secondary, and tertiary types and were usually derived from several of the patent vessels. They generally followed a tortuous course and were thus easily distinguished from noncollateral vessels nearby. Although the majority of these anastomoses were embedded in myocardium or in ischemic scars thereof, some were epicardial and easy to dissect out in toto. They occasionally formed a leash immediately about the occluded coronary segment. In a few instances they were observed in areas of the endocardium at the borders of, or overlying, healed infarcts (Fig. 12). In the left ventricle and the interventricular septum they were often too entangled to count in the angiograms (Fig. 10). Their number and size showed some degree of inverse interrelationship, in that the largest of the anastomoses tended to be solitary or complemented with only a few small ones (Fig. 11).

Anastomoses associated with recent occlusive coronary lesions were intermediate in number, size, and distribution between those which bypassed healed occlusions, and those which bypassed coronary ligations.

Discussion

The experiments described here show that (1) Intercoronary arterial anastomoses probably exist in most adult human hearts. (2) These anastomoses connect major divisions of the coronary tree, different branches of the same division, and different segments of the same coronary branch. (3) In the absence of occlusive coronary artery disease, anastomoses are few and spotty in distribution. (4) In the presence of coronary occlusions, anastomoses enlarge and increase in number between the occluded vessel and the rest of the coronary tree.

The old controversy which persists about

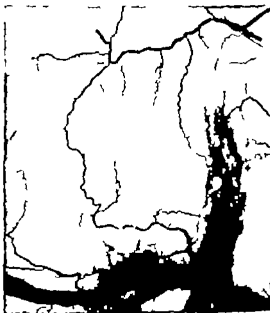


Fig. 6. Right atrial portion of coronary angiogram of unrolled heart of Group A with severe (+++) coronary narrowing. Large vessel at bottom of photo is right coronary artery. Smaller vessel at top of photo is sinoatrial artery which originated from the left circumflex coronary artery. A large anastomotic channel joins the right coronary and the sinoatrial artery. Positive print ×1.

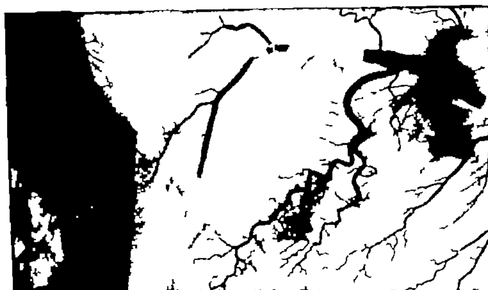


Fig. 7. Portion of angiogram of unrolled normotrophic heart of Group B with slight coronary narrowing. Ligated right coronary artery and left anterior descending coronary artery are shown. Distal segments of both each filled via anastomoses from the proximal segment of the left anterior descending coronary artery. Compare with Figs. 8, 9, and 10. Positive print ×1.



Fig. 8. Portion of angiogram of unrolled heart of Group B (350 grams), showing ligated, severely calcific and stenosed right coronary artery. Distal segment filled via primary anastomoses derived from septal branches of left anterior descending coronary artery. Retrograde filling of distal segment does not appear to be any greater in extent than that in heart shown in Fig. 7. Positive print ×1.



Fig. 9. Portion of unrolled heart of Group A showing right coronary artery which was obstructed by fresh thrombus at point indicated (arrow). Primary anastomoses from septal branches of left anterior descending coronary artery conveyed mass into distal segment of occluded vessel. A branch of the latter in the free wall of the right ventricle was retrogradely injected via primary anastomoses from the left anterior descending coronary artery which traversed the moderator band. Compare with Figs. 8, and 10. Positive print ×1.

the first conclusion listed above has been ascribed often to methodological differences among investigators. Nevertheless, it is evident that workers employing different methods can agree on the incidence of intercoronary arterial anastomoses in normal human hearts. Thus, the opinion that the incidence is low is shared by Zoll and associates,[1] who used Schlesinger's technique,[4] and Pitt,[12] who used spherules; the opposite view is held by Spalteholz,[13] who cleared injected specimens, by Cross,[...] who used stereoangiography,[...] and by Baroldi and co-workers,[3] who examined casts.

The study reported here illustrates variance in results obtained with different methods of study. It was shown that the manifest incidence of anastomoses differs according to whether Schlesinger's criteria[4,5] or angiography is relied upon to detect anastomoses and according to whether coronary arteries are ligated prior to injection. Since it was the same series of hearts that was studied in different ways, the variance in the results that we obtained would seem to reflect differences in the effectiveness with which anastomoses were detected by the various methods that we have used. With much the same explanation in mind, it appears that data published by workers on opposite sides of the controversy about the incidence of human intercoronary arterial anastomoses can be mutually comprehensible. Of course, with regard to their two views on the matter, only one is correct, and the interpretation of the results adduced in support of the other view must be in error.

In the subsequent paragraphs, the focus is mainly on an assessment of the results that we and others have obtained by applying Schlesinger's criteria for anastomoses. A brief discussion of certain objections against the validity of the stereoangiographic method in studies such as we describe here is given in a closing section.

Important data interpreted as supporting the view that anastomoses (at least 40 micra in diameter) are absent in the majority of adult human hearts are those of Zoll and associates.[1] In a series of over 1,000 hearts studied by Schlesinger's original technique,[4] these workers discovered anastomoses in a small proportion of hearts without coronary occlusions. This result was confirmed here by using a similar

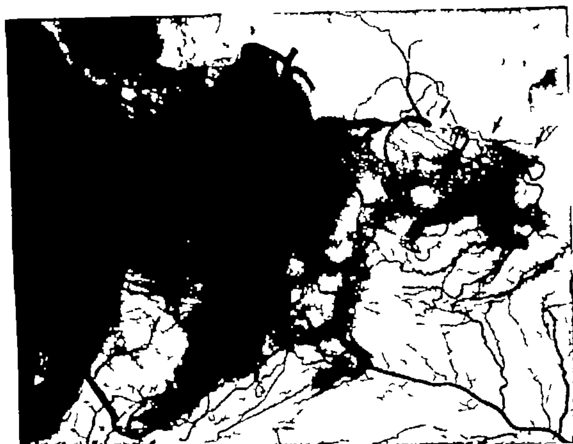


Fig. *10*. Portion of coronary angiogram of unrolled heart of Group A with a healed occlusion (*arrows*) in the proximal part of the right coronary artery. Distal segment of this vessel filled retrogradely and completely from the left anterior descending coronary artery via numerous anastomoses in the interventricular septum and the free wall of the right ventricle. Compare with Figs. 9, 8, and 7. Positive print ×1

method of study in Group A (no ligations) but we are not inclined to agree with the interpretation given. The latter requires the assumption that anastomoses are absent if they are not detected in a heart thus examined, and this assumption does not seem to be justified by a critical evaluation of the technique used or by other results obtained in this study.

Zoll and co-workers themselves point out that "in its original version Schlesinger's technique does not allow one to detect all anastomoses (pervious to the injection mass) in each of the hearts processed."[18] The same can certainly be asserted for the version of the technique used in Group A. In accordance with their criteria[4] anastomoses are considered to be present if (1) these are dissected in toto, or if it is certain that retrograde injection has taken place because (2) mass is found distal to a coronary obstruction or (3) mass injected into one coronary ostium is detected (by its color) in vessels supplied from the other ostium. Since full dissection of anastomoses is often impractical, it would appear that in hearts so studied without coronary obstruction any number of large nondissectable anastomoses—between the left anterior descending and the left circumflex coronary arteries, between different branches of the same major coronary artery, and between different segments of the same coronary branch—all regularly escape detection because the vessels conjoined by these anastomoses are injected from the same coronary ostium with the same colored mass. In such hearts, the successful detection of large nondissectable anastomoses by Schlesinger's method requires both of two



Fig. 11. Interventricular septal part of coronary angiogram of unrolled heart of Group A with old occlusion (*line*) in proximal part of left anterior descending coronary artery. Occluded vessel filled via large tortuous anastomotic channel (*arrow*) from the posterior descending branch of the right coronary artery. Positive print ×1.

conditions: first, that the anastomoses connect the left and right coronary arteries, and second, that adequate pressure differentials develop during injection to force the mass from one side of the coronary tree through to the other.

Provisions for meeting the second condition are distinctly better in Schlesinger's original technique[6] than in the version used in Group A. He employed lead phosphate agar as the injection mass, instead of barium sulfate-gelatin.[7] Although both these masses can penetrate arterioles of similar size,[7] the former is less viscous and therefore lends itself more easily to retrograde flow than the latter. Both versions begin with injection pressures which are equal for the left and the right coronary ostia. Whereas we kept these pressures equal throughout the procedure, Schlesinger unbalanced the injection terminally in order to induce high intercoronary pressure gradients for contralateral anastomotic flow. That is to say, he alternately reduced the pressure to 0 mm. Hg, first in one side of the coronary tree and then in the other. In these differences between the two versions of his method there is perhaps some reason for the fact that in Group A (no ligations) we could not duplicate the results of Zoll and associates,[11] who found a large proportion of hearts with anastomoses in cases of anemia, cardiomegaly, valve deformity, and cor pulmonale. It is stressed here that our findings are not against the concept that anastomoses increase in size and number in these conditions of relative cardiac anoxia, but are merely against the opinion that, to begin with, no anastomoses pervious to the mass exist in most human hearts.

Although the alternate reduction of injection pressures in the two sides of the coronary tree favors, no doubt, the contralateral anastomotic flow of mass, the timing of this particular maneuver in Schlesinger's original technique[6] seems to provide grounds for the suspicion that such a flow may not invariably occur in hearts in which the appropriate anastomoses are limited. Late in the injection procedure, resistance to the contralateral flow is magnified, probably to a considerable degree, by the presence of the mass introduced earlier into the side of the coronary tree receiving the flow. It would seem that this mass could very well hold back that which traverses and issues forth from the anastomotic passages. It appears that Reiner and co-workers[17] have the same doubts about the reliability of this terminal unbalancing of injection pressures for effecting contralateral flow of mass in normal specimens.

In the presence of coronary occlusions, the chances for the detection of whatever anastomoses exist in a given heart are with either version of Schlesinger's method technically very much improved. For one reason, the nondissectable anastomoses



Fig. 12 Photograph of endocardial aspect of base of left ventricle. The posterior leaflet of the mitral valve has been reflected to show macroscopic intercoronary arterial anastomoses in endocardium overlying ischemic scar of myocardium. Cut surface of myocardium shows pale areas of fibrosis.

which according to the set criteria, it is possible to detect are no longer confined to those between the left and right coronary arteries, but now include also those between the obstructed vessel and the rest of the coronary tree. For another reason, the occlusion itself mechanically insures that during injection maximum pressure gradients conducive to anastomotic flow develop consistently between vessels with direct access to the source of the perfusion and the occluded artery in which the pressure is nil. It would appear that from points of partial coronary obstruction or stenoses lesser mechanical effects which similarly favor anastomotic flow are also derived

In the hearts of Group B some vessels were ligated prior to injection so that the intercoronary pressure gradients which later developed would be comparable to those in specimens in Group A with occlusive coronary artery disease The results which showed that in each heart in Group B anastomotic injection occurred in at least one of the ligated vessels make it appear rather more than less likely that anastomoses pervious to the injection mass exist in most human hearts, and that in hearts of Group A with coronary occlusions, at least one reason why anastomoses were often detected by Schlesinger's method was purely technical Conditions for discovery were better in hearts with occlusions than in those without.

Other methods involving the injection of a single coronary trunk (or branch) would appear to similarly favor the detection of anastomoses in normal specimens. With these methods, parts of the coronary tree excluded from direct injection are in effect, obstructed at their origins. The high intercoronary pressure gradients which develop as the hearts are being injected provide conditions favorable for anastomotic flow of mass between directly injected and excluded vessels. Probably because of the high pressure gradients induced in normal hearts studied with these methods, many workers, using different injection materials and levels of pressure were often able to detect anastomoses between the left and the right sides of the coronary tree.[17, 22] We are

at a loss to account for the fact that some unilateral perfusion experiments which have been described[9,13] yielded results similar to those pertaining to the nonligated hearts of this series (Group A) and those obtained by others[22-25] who, as we, used bilateral coronary injection techniques patterned after that of Schlesinger.

It is to be noted that the anastomoses detected by the method of injecting a single coronary artery are largely restricted, by technical design, to those which conjoin directly and indirectly injected vessels. To be sure, the same restriction holds true for the ligation-injection method used in Group B. However, this latter method does seem to have an advantage in that the coronary tree is ligated at several points. This feature in its technical design multiplies the intercoronary border zones across which anastomotic flow is induced to occur, and enhances thereby, possibly to a corresponding degree, one's chances of finding the anastomoses present in a given specimen. Since ligations can be positioned so as to simulate closely the distribution of pathologic occlusions, the latter method also seems to be better suited for the comparative study of anastomoses in normal hearts and in those with occlusive coronary artery disease.

Although anastomoses pervious to the injection mass seem to be present in most human hearts, those found here in specimens *without occlusive coronary artery* disease appeared to be generally small, few, and spotty in distribution, whereas those associated with healed occlusive coronary lesions were large, numerous, and strategically concentrated to bypass the occlusions. These differences between "normal" and "abnormal" anastomoses were assessed by comparing the incidence and extent of retrograde injection distal to natural and artificial coronary obstructions, and by direct visualization of the anastomoses in the coronary angiograms. Both kinds of evidence were mutually confirmatory.

The volume of anastomoses around healed occlusions was shown to be large by the fact that retrograde injection from adjacent patent vessels occurred invariably and extensively beyond such lesions. In contrast, ligated vessels in hearts free of occlusive coronary artery disease were often found to be incompletely filled with mass—indicating that the anastomotic routes leading into them were limited, and in a number of specimens, only one or two of the (three) ligated vessels of each contained any mass—indicating that such routes as did exist were unevenly distributed in the coronary tree. The observation that both the incidence and extent of retrograde injection into ligated vessels were not demonstrably improved in the presence of severe coronary narrowing or cardiac hypertrophy suggests that with these conditions, the increase in the volume of anastomoses, if any, is not very great. The fact that most of the ligated vessels free of mass proved to be coronary branches rather than main stems seems to reflect the spotty distribution of the anastomoses in the coronary tree without occlusive lesions. The smaller the vascular territory excluded from direct injection, the greater the chances seem to be that none of the few anastomoses scattered about will be interposed between the injected and the excluded vessels. It is of interest to note that Schlesinger[4] did not observe retrograde injection in hearts in which small arteries had been ligated, whereas most other workers[7,12] who excluded large portions of the coronary tree from direct injection often succeeded in a similar search. Laurie[1] has recently called attention to individual variations in the distribution of anastomoses between major coronary arteries.

In pathophysiologic terms, it appears that certain points can be drawn from the observations just discussed. The point which the selective filling of ligated vessels seems to illustrate is that, in vivo, the existence of large intercoronary arterial anastomoses in a given heart does not, in itself, guarantee any protection against the effects of a subsequent block developing in the coronary tree. This protection is contingent upon the topographic relationship which the anastomoses will have with the supervening occlusion. Such anastomoses protect if they happen to conjoin occluded and nonoccluded vascular territories, but not if their interconnections lie entirely within either one of these territories.

Another point concerns the anastomoses which develop sometime after a coronary occlusion has taken place and which are strategically positioned for the diversion of

blood past the latter. It would appear that the major benefit to be derived from these anastomoses does not accrue to areas of the myocardium distal to the occlusion—by the time such anastomoses are fully developed these areas are largely past the need for them—but accrues rather to other areas supplied by such of the patent vessels as are joined by anastomoses to the occluded artery. If one of these sources of anastomotic flow becomes blocked in turn, the artery first occluded is then in a position to relay to it part of the blood received from the others.

Macroscopic anastomoses were identified in stereoangiograms by Gross, Campbell,[25] Vastesaeger and associates,[31] and Bellman and Frank.[29] From their respective observations, these workers concluded that gross anastomoses exist in most human hearts, that such anastomoses occur not only between the left and right coronary arteries but also between different branches of the same coronary artery, and that anastomoses increase in size and number between the occluded artery and the rest of the coronary tree. In the angiographic survey of our material, we found support for the third and the second conclusions and discovered no reason to take exception with the first.

Although we failed to identify gross anastomoses in the angiograms of the majority of the hearts in Group A (no ligations), this failure can be attributed less to the absence of anastomoses and more to the *limitations of the angiographic method for detecting anastomoses.* With regard to these limitations, Zoll and associates made two points. The first is that anastomoses which are not visible in the coronary angiograms can on occasion be clearly demonstrated by dissection; the second is that overlapping vessels, like bare branches of adjacent trees, often deceptively give the angiographic appearance of intercommunications. Because of the first point we have refrained from concluding that gross anastomoses were absent in instances in which these were impossible to identify in the angiograms. We also deferred to the second point. Although angiographic appearances can be deceptive and true at the same time, our survey purposely favored parts of the heart with little vascular overlap, and only those anastomoses whose nature could not be questioned were included in the tally. These precautionary measures that we have taken no doubt distort our results so as to provide (a) an inaccurate picture of the distribution of gross anastomoses in various regions of the heart, (b) an underestimate of the number of hearts with macroscopic anastomoses, and (c) an underestimate of the number of such anastomoses in any of the specimens examined. Because of the limitations of angiography, the fact that we were unable to note significant differences in the number of anastomoses in hearts with and in those without certain conditions of cardiac hypoxia probably does not rule out such differences.

Summary

Four hundred and seventy adult human hearts from patients 13 to 96 years of age were studied angiographically using barium sulfate-gelatin injected at 200 mm. Hg for 5 minutes (modified Schlesinger method). In 40 hearts, some coronary arteries were ligated and transected before injection; in another 430 hearts, no ligations were made.

Intercoronary arterial anastomoses were detected in two ways: (1) by stereoangiography and (2) by applying Schlesinger's criteria (i.e., anastomoses are considered to be present if dissected in toto or if mass appears beyond a coronary obstruction or if mass injected into one coronary enters another).

By Schlesinger's criteria, anastomoses were present in almost all hearts with coronary occlusion or ligation and absent in most of the other hearts comprising the bulk of the series. Cardiomegaly, valve deformity, cor pulmonale, and anemia did not increase the incidence of anastomoses detected.

Stereoangiography disclosed macroscopic anastomoses in all hearts with natural or artificial occlusions and in many hearts which fulfilled none of Schlesinger's criteria. These anastomoses connected major coronary divisions, or different branches of the same division, or different segments of the same branch. Anastomoses in hearts without occlusive coronary artery disease were

*Slightly modified from an abstract by F. L. Rodriguez, S. L. Robbins, and M. Rabinowitz which appeared in Circulation XXVIII, No. 4, Part II, October 1963, page 793, by permission of the American Heart

small few and spotty in distribution. Those associated with old occlusions were enlarged numerous and strategically concentrated to bypass occlusions.

This study suggests that (1) intercoronary arterial anastomoses exist in most adult human hearts (2) the demonstration of anastomoses by Schlesinger's method is mechanically favored by coronary occlusions natural or otherwise (3) current controversy in regard to the incidence of intercoronary arterial anastomoses in normal human hearts stems from the error of equating absence of anastomoses with inability to detect them.

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The interchangeability of vectorcardiographic systems

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Because of the great number of vectorcardiographic systems now clinically applied, an obvious need for the transfer of information obtained with one system into a form interpretable by users of another system has arisen. Burger[1] has proposed the determination of coefficients of transformation based on the solution of simultaneous equations for values of voltage obtained in selected instants of recording with two or more sets of vectorcardiographic leads. He examined the degree to which such transformation from one vectorcardiographic system to another can be obtained by applying the reciprocals of the transformation coefficients as resistances in a transformation network between the vectorcardiographic leads and the vectorcardiograph.

We approached the study of this transformation between systems with two purposes. First, we were concerned about the variation in dipolar-multipolar content of the heart signal throughout the heart cycle.[2-4] By utilizing many sampling points evenly spaced throughout the QRS complex, we sought to minimize variation which might arise from the limited selection of only three to five sampling instants. Second, we wished to know whether the apparent variation between normal individuals in their transformation coefficients from one system to another related to any clinically obvious anatomic or electrophysiologic parameter—such as height, weight, or electrical axis. (The anatomic lie of the heart was not included for study because its determination is beset with inconsistencies well outlined elsewhere.[5])

Methods

For each of 35 normal young men (with a mean age of 24.5 years and standard deviation of 4.2 years) the appropriate vectorcardiographic leads of the SVEC III,[6] axial,[7] and Frank[10] systems were recorded simultaneously from the face of an eight-channel oscilloscope by means of a Grass kymograph camera.[11] Because the Y leads of SVEC III and of the McFee Parungao axial systems are identical except for scaling or gain factor, only the latter one such lead was recorded. The photographic recordings (Fig. 1,A) were then carefully processed by

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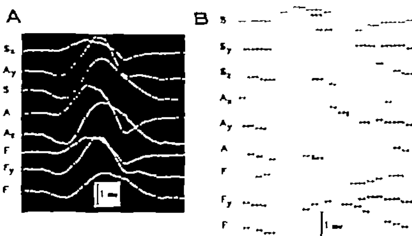


Fig. 1. Comparison of high-fidelity, high-speed simultaneous recording of the QRS complex in 8 orthogonal leads from a normal 27-year-old man (A) with the digital reconstruction of the leads of these orthogonal systems from measurements made at 2.5-msec. intervals (*B*). Note that the Y lead of the SVEC III system was not recorded separately because it is equivalent to the Y lead of the McFee-Parungao axial system at 0.71 strength.

an oscillographic analog-to-digital converter at the Data Processing Center of the McDonnell Aircraft Corporation in St. Louis, Missouri, so that simultaneous potential values were obtained on punch cards at a sampling rate of 390.0 per second during the inscription of a selected QRS complex. A scaling factor of 0.71 was applied to the unweighted Y lead of the axial system to obtain the Y for the SVEC III. The digitized representations of the three leads of each system can be seen plotted as waveforms in Fig. 1 *B*. Next, a least-squares approximation giving the best fit for all instants in the QRS complex was obtained for the transformation between systems for each subject. The basis for the computer programming lay in the following relationship.

We sought to find the coefficients r_{11}, r_{12}, r_{13} which specified how much voltage of each lead (x, y, or z) of system A was to be found in a given lead (x, y, or z) of system B in order to perform a transformation from system A to system B.

In mathematical terms one solves for the coefficients of synthesis, r_{1}, r_{12}, and r_{13}, which best satisfy the idealized relationship

$$b(t) = r \; a_1(t) + r \quad (t) + \quad (t),$$

where b (t) is a representative member of the lead set which is to be fitted by the second set $a_1(t)$, $a_2(t)$, and $a_3(t)$.

The individual leads are represented as continuous functions of time in the preceding equation. For purposes of solution by digital computer each continuous function is approximated by a set of discrete values determined at equal increments of time, Δt. In this digitized form b_k, for example, would be the kth value of the number set representing b (t). For a three-to-three transformation the foregoing equation becomes

$$\begin{aligned} b_{1k} &= r_{11} a_{1k} + \quad a_{2k} + r \; a_{3k} \\ b_{2k} &= r_{21} a_{1k} + r_{22} a_{2k} + r_{23} a_{3k} \\ b_{3k} &= \quad a \; + r_{32} a_{2k} + r_{33} a_{3k} \end{aligned} \tag{1}$$

It is the coefficients, r, which specify the transformation of lead set, A, into lead set B (*i. e.*, *the synthesis of B from A*).

Written in more compact notation, Equations 1 become

$$b_{ik} = r \quad a \qquad i, j = 1,2,3 \qquad k = 1,2,3 \; \ldots \; n \tag{2}$$

where *n* is the total number of samples or values into which each lead has been digitized. Equations 1 and 2 represent three sets of simultaneous equations from which may be determined the transformation numbers r_{ij}. A number of sampling instants *n* exceeding 3 indicates that there are more equations than unknowns, providing the opportunity for a statistical fit

of one lead set to the other The manner in which this fit may be obtained is indicated by the following development.

Equation 2 may be rewritten in matrix notation as

$$\underset{B}{(3\times n)} = \underset{R}{(3\times 3)} \underset{A}{(3\times n)} \quad (3a)$$

where the notations in parentheses indicate the dimensions of the individual matrices. Postmultiplying both sides by A^T the transpose of A gives

$$B A^T = R A A^T \quad (3b)$$

and then postmultiplying both sides of Equation 3b by the inverse of AA^T gives the desired solution

$$R = B A^T (AA^T)^{-1} \quad (3c)$$

The elements, r of matrix, R are the coefficients which provide a least-squares fit of B leads by the A leads Conversely the inverse matrix, R^{-1} specifies the best fit of the A set by B leads.

Thus, a computer program was designed to form two correlation matrices first BA^T comparing the leads of B with those of A, and second AA^T comparing the leads of A with themselves. This latter matrix was inverted $(AA^T)^{-1}$ and when premultiplied by the first correlation matrix yielded the transformation matrix R.

Upon obtaining the values of R for each of the six transformations between the three systems under study we instructed the digital computer to determine the correlation coefficient between each component value of R and other individual characteristics such as the height, weight age, surface area and an index of obesity * For all values of the correlation coefficient greater than 0.6 an XY plot was punched out for inspection In addition mean values for the group (with standard deviations) were determined for each transformation e.g the average value of the transformation coefficients in the SVEC III to-Frank transformation was obtained by totaling the corresponding coefficients for all subjects and dividing by 35 Standard deviation was then determined in conventional fashion

Cross-correlation between any two simultaneous QRS waveforms subtending equivalent areas was estimated by dividing the sum of the products of corresponding instantaneous amplitudes by the sum of the squares of the instantaneous amplitudes of one member of the pair Correction for waveforms of differing areas was made by multiplying the result by the square root of the ratio of areas (or more practically the square root of the ratio of sums of squares of instantaneous amplitudes.) A waveform compared with itself or with an identical twin would yield a value of 1 0 indicating perfect cross-correlation poor cross-correlation would be indicated by values approaching zero

Finally all eight waveforms for each subject were treated as an information pool which was then subjected to principal factor analysis[†] Factor analysis compares each of a population of waveforms with every other waveform in the group, retains the several bits of unique information and eliminates the redundant information recurring in lead after lead The amount of each principal factor describing the information in the waveform for each orthogonal lead was determined

Results

The average transformation coefficients and their standard deviations for conversion between each of the three vectorcardiographic systems (SVEC III axial and Frank) are shown in Table I Thus, for line 1 in the table indicating the conversion from the SVEC III to the axial (McFee Parungao) system we may interpret the values as indicating that *on the average* the values of the coordinates of any given point S_x in a SVEC III vectorcardiographic loop may be multiplied by the appropriate coefficients to determine the location of the corresponding point $A_{x,y,z}$ on the simultaneous axial loop. Fig 2 illustrates geometrically this principle of transformation and Figs 3A C demonstrates its application Note the degree of disparity between the Frank loop constructed from the simultaneously recorded values and one obtained from applying the *average* transformation coefficients to the digitized SVEC III lead

*The obesity index was set equal to the cube root of each subject's mass in kilograms divided by the subject's height in centimeters.

†These cross-correlation indi

Table I

Input	*Average transformation coefficients (with standard deviations)*									*Output*
	X			Y			Z			
	x	y	z	x	y	z	x	y	z	
SVEC III	1.83 ± .45	0.54 ± .50	0.14 ± .17		1.41 ± .00		−0.68 ± .44	−0.20 ± .32	1.15 ± .14	Axial
Axial	0.40 ± .14	−0.00 ± .18	−0.07 ± .05		0.71 ± .00		0.27 ± .18	0.04 ± .21	0.82 ± .12	SVEC III
SVEC III	1.04 ± .72	0.38 ± .42	0.11 ± .11	−0.10 ± .29	1.14 ± .30	0.18 ± .07	−0.28 ± .47	−0.07 ± .35	0.98 ± .21	Frank
Frank	0.64 ± .21	−0.05 ± .16	−0.07 ± .10	0.18 ± .24	0.66 ± .26	−0.12 ± .08	0.23 ± .30	−0.00 ± .31	1.01 ± .27	SVEC III
Axial	0.63 ± .15	0.03 ± .14	−0.00 ± .07	0.04 ± .14	0.77 ± .25	0.15 ± .07	0.12 ± .23	0.07 ± .22	0.81 ± .18	Frank
Frank	1.40 ± .28	0.09 ± .17	−0.06 ± .17	0.25 ± .34	0.93 ± .37	−0.16 ± .11	−0.26 ± .34	−0.05 ± .27	1.24 ± .30	Axial

The coefficients listed in the table summarize the average simultaneous equations of transformation, e.g., the first line illustrates transformation from SVEC III leads to Axial (McFee) leads:

$$A_x = 1.83S_x + 0.54S_y + 0.14S_z$$
$$A_y = 1.41S_y$$
$$A_z = -0.68S_x - 0.20S_y + 1.15S_z$$

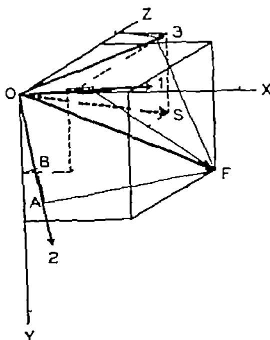


Fig. 2. Diagram representing coefficients of transformation as vectors of transformation. The values in the fourth line of Table I may be expressed by the simultaneous equations

$$S_X = 0.64\,F - 0.05\,F - 0.07\,F \quad (1)$$
$$S_Y = 0.18\,F + 0.66\,F_y - 0.12\,F \quad (2)$$
$$S_Z = 0.23\,F - 0.00\,F + 0.01\,F \quad (3)$$

For example, transformation vector 2 has as its Cartesian coordinates the values in Equation (2) above. Thus, if a point F on the vectorcardiographic curve recorded by the Frank system is to be transformed to the SVEC III, the following geometrical interpretation may be made. Each new coordinate of the transformed point results from the dot product of the vector to the original point F and a transformation vector. Thus, Equation (2) is rewritten, $S_Y = F \cdot T_Y$. In the diagram transformation vectors T, T_Y, and T are labeled 1, 2, and 3 respectively. Geometrically the dot product may be visualized (as with vector 2 above) by dropping the perpendicular from point F to vector T_Y, i.e., obtaining the projection OA of vector F on vector T_Y. Then the numerical value of the length of this projection OA is multiplied by the numerical value of the length of the vector T to obtain the length of the desired product S_Y (represented by line segment OB). Since $T = \sqrt{(0.18)^2 + (0.66)^2 + (-0.12)^2} = 0.76$, $S_Y = OB = 0.47 \times 0.76 = 0.36$. This new value is then transferred to the Y axis and, similarly, the values for S_X and S_Z are obtained to determine (as shown with the broken-line box) the position of the simultaneous transformed point S (indicated by the broken-line arrow.)

values. Note how much closer to the original is the reconstructed loop if the subject's own individual least-squares fitted coefficients are employed.

Some estimate of the variation between individuals can also be obtained by examining the spatial scatter of coefficients when they are treated as vectors. An example is shown in Fig. 4. The transformations between the various systems were of the same order as shown here except for the Y lead common to both SVEC III and axial systems. As expected, transfer between these two systems—as to the Y leads only—consisted of either lengthening or shortening the transformation vector lying on the Y axis to 1.41 or to 0.71, respectively, as appropriate.

Examination was made of the correlation between components of the transformation vectors (either in Cartesian or spherical coordinates) and certain other readily ascertainable characteristics: height, weight, age, surface area, an index of obesity, the magnitude, altitude, and azimuth of the mean spatial axis of either the given or the desired vectorcardiogram. With two exceptions all the correlation coefficients were less than 0.6, and none was greater than 0.7. In contrast, for corresponding components of the mean axis (either Cartesian or spherical) the correlation coefficient ranged between

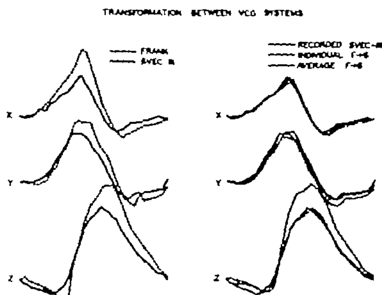


Fig. 3A. Comparison of simultaneous X, Y, and Z leads obtained by the Frank (*broken line*) and SVEC III (*solid line*) vectorcardiographic reference systems, and a comparison of the transformations from Frank to SVEC III by using both the individual subject's own transformation coefficients and the average transformation coefficients for the whole group of 35 normal subjects. This particular subject was chosen for illustration because his individual 9 transformation coefficients each differed in value from the mean by about one standard deviation.

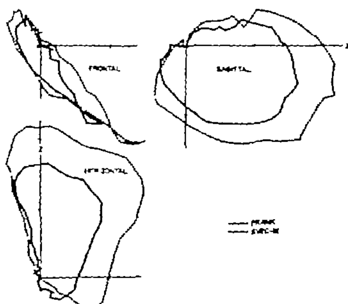


Fig. 3B. Comparison of the frontal, sagittal, and horizontal plane projections of the Frank and SVEC III vectorcardiographic loops of the same subject. These were derived from the leads shown in the first panel of Fig. 3A.

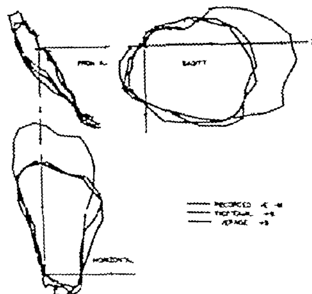


Fig. 3C. Comparison of the plane projections of the recorded SVEC III vectorcardiographic loop with two loops calculated by transformation from Frank X, Y and Z leads for that subject. Note the difference between the relatively good approximation obtained with the subject's individual transformation coefficient and the poorer approximation obtained with average transformation coefficients.

0.8 and 0.9. (For example components of the mean axis of the SVEC III and Frank systems correlated to the level of r = 0.84 for magnitude, 0.83 for altitude, and 0.88 for azimuth.) Of interest, however, were two vague trends. One suggested a possible relationship between the relative amount of Frank z needed to form axial Z and the body weight (r = 0.68) as shown in Fig. 5. In contrast, there was a lack of such suggestion of relationship between the corresponding component of the reverse transformation (i.e., axial z in Frank Z) and the weight (r = 0.46) or any of the other physical parameters. A second possible relationship was noted between the relative amount of axial z required to form SVEC III and the azimuth of the mean spatial axis of the axial leads (r = 0.65).

Table II shows the mean cross-correlations between waveforms as recorded by the different orthogonal systems. (As indicated earlier, perfect cross-correlation, as might be expected between two identical waveforms, would be represented by a value of 1.0, and no cross-correlation by a value of zero.) Note the expected very good correlations with small standard deviations between the X leads of each system, and similarly between the Y leads and between the Z leads. However, note also the rather good correlation between X and Y leads, as well as the additional suggestion of kinship between Frank Y and Schmitt Z.

In Table III, the result of pooling all of the information available in the eight simultaneously recorded orthogonal leads is evaluated. In column 1, the average amount of the first principal factor waveform found in each lead is shown. Note that this factor was relatively "strong" in both X and Y leads but weak in Z leads. By contrast, the information in principal factor 2 was utilized mainly in the Z leads but with comparatively large individual variations.

Discussion

Limitations of the method. Continuous sampling at intervals of 2.5 msec. over the entire QRS complex instead of at three to five selected intervals has the advantage of providing a least-squares fit of the best transformation from one vectorcardiographic system to another throughout ventricular depolarization. Thus, whereas one system may be sensitive to certain nondipolar elements of the heart signal during portions of ventricular depolarization and the other system not sensitive to these elements of signal, the discrepancy between

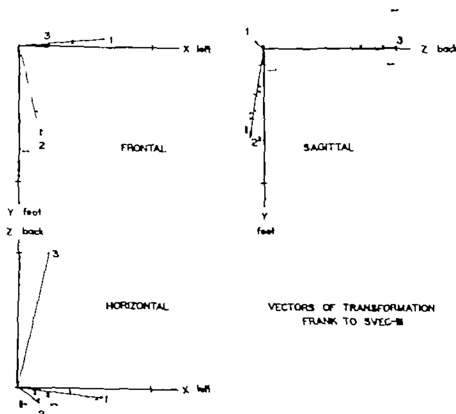


Fig 4 Scatter diagrams showing on frontal, sagittal, and horizontal plane projections the spatial distribution of the individual vectors of transformation for 35 normal young men for the transformation from Frank-to-SVEC III vectorcardiographic systems. The arrows indicate the average transformation vectors 1, 2, and 3 for the group. Note that the "clouds" representing each population are not spherical but are roughly ellipsoidal.

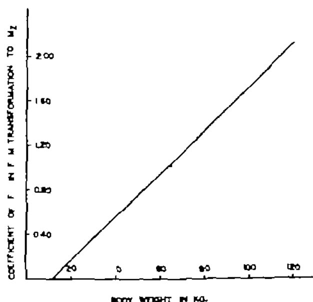


Fig 5 A plot demonstrating the relationship between the magnitude of the individual 9th transformation coefficients (amount of F in Az) in the Frank-to-axial transformation and the subject's body weight. The correlation coefficient r was 0 68. See text for details.

Table II. Waveform cross-correlations between three corrected lead systems

	Axial X	Frank X	SVEC-III-Axial Y	Frank Y	SVEC III Z	Axial Z	Frank Z
SVEC III X	9426 ± 0946	9378 ± 0987	8518 ± 1371	7448 ± 2213	1313 ± 4126	− 1573 ± 4407	0130 ± 4724
Axial X		9829 ± 0207	8820 ± 1318	8292 ± 1374	2640 ± 4336	− 0370 ± 4467	1363 ± 4849
Frank X			8785 ± 1371	8365 + 1571	2947 ± 4016	− 0087 ± 4181	1668 ± 4445
SVEC-III-Axial Y				9265 ± 1111	2870 ± 4328	0055 ± 4373	1783 ± 4338
Frank Y					4951 ± 3405	2553 ± 3680	3985 ± 3441
SVEC III Z						9253 ± 0607	9637 ± 0457
Axial Z							9598 ± 0473

Table III. Mean weighted transformation vectors and standard deviations from "signal space" to respective corrected X, Y, Z leads*

	Principal factor 1	Principal factor 2	Principal factor 3
SVEC III X	867 ± 144	− 225 ± 382	− 055 ± 163
Axial X	931 ± 097	− 047 ± 330	− 010 ± 107
Frank X	931 ± 080	− 056 ± 326	019 ± 122
SVEC-III Axial Y	916 ± 115	− 069 ± 338	− 004 ± 164
Frank Y	891 ± 149	075 ± 372	072 ± 187
SVEC III Z	393 ± 547	435 ± 604	− 017 ± 082
Axial Z	133 ± 579	473 ± 662	− 012 ± 072
Frank Z	290 ± 592	438 ± 621	− 003 ± 075

*"Signal space" refers to an arbitrary Cartesian reference frame whose axes are those of 3 major principal factors. These result from reduction of the waveform information in the 8 simultaneous leads to component orthogonal waveforms by means of principal factor analysis. Weighting was accomplished by multiplying the appropriate eigenvector components by the square root of the eigenvalue to yield in effect an estimate of the degree to which each factor contributed to the total information in the respective waveform. Thus, the total information in SVEC lead X for an individual subject might be represented by a vector with magnitude of 1.0 and direction in signal space indicated by the coordinates (.93, −.38, .08) and by the theorem of Pythagoras, $\sqrt{(.93)^2 + (.38)^2 + (.08)^2} = 1$. Note the wide variation (i.e., large standard deviations) for the signal space components of the Z leads as compared with the X and Y leads.

the two systems is minimized by averaging for the entire period of the QRS complex. A theoretical advantage of such a technique is that, if the sampling interval could be further reduced to 0.5 or 0.1 msec., then similar least-squares fits for segments of the QRS (for example, 10 msec. in duration) could be subjected to the same kind of analysis. In this event, one could examine whether variation in the characteristics of transformation occurs from one portion of the QRS cycle to another. A decrease in the sampling interval would also afford examination of the transferability of high-frequency components of the electrocardiogram from one system to another. It is

reasonable to expect that som ... the high frequency components rec ... lead but not in another may ... from local proximity effects or ... elements of the heart signal

The search for correlation between ... formation characteristics and body we... ... general the correlation between the ... acteristics of tran formation from one ... tem to another and that of any of the ph... cal parameters was poor so that variati... in the transformation coefficients should be considered to be random The clinical implication of this observation is that a network of fixed resistances would be an inadequate means of predicting for example the Frank vectorcardiographic loop for an input through the SVEC III lead set Furthermore individual adjustment of the transformation by varying the dial settings on an array of potentiometers according to readily ascertainable physical characteristics of the subject is out of the question However it is of interest that there was a slight trend toward relationship of the transformation coefficients with regard to total body weight. Just why the amount of Frank lead Z required to form axial lead Z should vary with the total body weight is unclear If in a greater number of subjects such a trend should persist one may suppose that the correlation of one system with the weight reflects a sensitivity to total body mass because of several possibilities (a) the resistive characteristics of the lead are vulnerable to the distribution of body fat (b) the relative position of the electrodes of the lead to the heart and the diaphragm may be altered by variation in total body weight (c) proximity effects may be accentuated by one lead system and be modifiable by body build i e. the more a subject approaches the spherical the more likely will certain placements of the lead electrodes produce remote leads, reduce multipolar contamination and promote dipole purity We think that it is not clear that any of these factors is operative for (a) correlation of the magnitude and orientation of the mean axis to body weight of one system with the other was not significantly better (b) each of the orthogonal systems represents a careful attempt at spreading the pickup over the body surface and weighting with resistances to obtain equivalent remoteness as much as possible and (c) the level of correlation was barely suggestive and by no means certain. However it is of interest that Hirsch and associates[13] have observed proportionality between lead vector magnitude and body weight in studies with the esophageal dipole triplet

The problems of weighting and orthogonality of lead systems Upon noticing the ellipsoidal geometry of the clouds of transformation vectors (Fig 4) we wondered whether the nonspherical shapes of these clouds may have been the result of the differences in lead weighting factors For example in a recent estimate of departure from unity in the three lead vectors for X Y and Z for each of these lead systems in the homogeneous torso model the axial system was found to be weighted 1 606 1 476 and 2.240 as compared with 1.286 1 048 and 1.545 for SVEC III and 1 448 1 395 and 1.371 for Frank. Thus, correction for weighting differences could be computed from ratios of these values. Such corrections were performed on the transformation vectors, but although individual points shifted the clusters remained ellipsoidal and of the same general size and orientation. We concluded that differences in weighting factors were not significant contributors to *variation* in transformation characteristics.

The transformation coefficients (either individual or average) in no instance formed a set of orthogonal vectors Thus, if transfer between any two members of the group of three so-called orthogonal vectorcardiographic systems was not accomplished by an orthogonal transformation it follows that at least two of the vectorcardiographic systems are *not* truly orthogonal We suspect that all three are imperfect and have no absolute standard of reference for the living human body although recent critical re-evaluation of these systems in the homogeneous torso model implies greater approach to orthogonality with the McFee-Parungao axial system than with the others.[12]

One of the reasons for failure of orthogonal transformations between systems ... viously lies in the respective anatomic placements of ... ctrodes ... permit cross-contam... ... of l... ... one ...

tem as compared with another For example the deliberate inclusion of a back electrode in the vertical or Y lead array of the Frank system would be expected *a priori* to produce considerable detection by Frank lead Y of signal found in the Z leads of all three systems as indeed is noted in the Frank Y row of Table II

The relationship of the vectorcardiographic leads to a common signal space Although the pool is by no means an estimate of the total information available,[4] we believe that principal factors 1 and 2 of the small pool probably do approach those determinable from extensive body mapping and that the long axis of the QRS spatial vector loop[5] approaches that of the spatial axis for principal factor 1 waveform We have used the small factored pool of 8 normalized corrected-othogonal vectorcardiographic leads as a reference signal space for a convenient estimate of the dipolar signal. If this assumption is correct, the clinical electrocardiographer would then expect both X and Y leads to reflect large amounts of principal factor 1 (lying along the electrical axis of the QRS complex) but the Z component to be individually variable As noted in Table III this was indeed the case. Similarly since the minor axis of the normally oriented spatial vector loop lies more or less parallel to the antero-posterior or Z axis high content of principal factor 2 in the Z leads is also a consistent finding In general the McFee Parungao axial leads were purer reporters of principal factor 1 in leads X and Y and principal factor 2 in lead Z than were those of the other systems. This is in keeping with the observation[4] that the principal factor loop derived from extensive recording in a normal subject was better reproduced by the axial lead system than by other currently employed vectorcardiographic lead systems

Summary

The simultaneously recorded QRS complexes of the scalar leads of three orthogonal vectorcardiographic systems (SVEC III Frank, and axial) have been converted to digital form and examined by means of computer analyses for the characteristics of transformation between any two systems in 35 normal subjects. A set of individual transformation coefficients fitted by the method of least-squares for the entire phase of ventricular depolarization in each subject was obtained so that when applied to the voltages of one lead system the configurations of the QRS complex in the leads of the other system could be closely approximated

There was however considerable variation within the group so that *average* transformation coefficients for the normal subjects sometimes gave very poor approximations of the desired set of scalar leads and vector loops from a given set An attempt was made to determine whether this variation in transformation characteristics depended upon certain physical parameters, such as height, weight age body surface area relative obesity or orientation of the mean spatial electrical axis of the QRS Mild trends were noted toward relating the components of Z in the Frank to-axial transformation to body weight and of the components of Z in the axial to-SVEC III transformation to the orientation of the mean spatial axis of the axial vectorcardiogram otherwise, the variation in transformation coefficients appeared to be random

Our tentative conclusion is that although interesting approximations can be obtained in the laboratory from the knowledge of average transformation coefficients, the practical interchangeability of quantitative information obtained from one lead system into that obtainable by another is seriously limited because of the wide range of biologic variation in transformation characteristics

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Evaluation of the angiotensin skin test

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The recent availability of synthetic angiotensin II has considerably spurred the investigation of the role played by this substance in hypertension and allied diseases. The first paper concerning the clinical suitability of the angiotensin skin test appeared in 1960.[1] In this work, a definite difference was observed in the response of hypertensive subjects to intradermally injected angiotensin when compared with that of normotensive patients. This was then confirmed by the same author 2 years later.

To explain the difference in response it was postulated that patients with hypertension may lack at the dermal level some enzymatic system (angiotensinases) which normally destroys vasopressor substances. By measuring the persistence of blanching, it was further speculated that one might indirectly measure the presence or lack of such an enzymatic system, as well as the reactivity of the small vessels to angiotensin, in normal and hypertensive subjects.

Since this first report, two others[3] have appeared which did not confirm the results observed by Jablons.[2] Recently, however, Mullane[4] has reported a definite delay in the blanching time in hypertensive patients and in alcoholics with abnormal liver function (mean = 116 and 93 minutes, respectively) when compared with that in normotensive subjects (mean = 59 minutes ± 36).

The purpose of the present investigation was to evaluate further the reliability and the eventual clinical application of this test.

Materials and methods

One hundred and eighty subjects, both male and female, were studied. Ninety-six were normal or affected by diseases not involving the cardiovascular system. Eighty-four patients were hypertensive. These were grouped as follows: (1) essential hypertension (asymptomatic and symptomatic) 63; (2) renal hypertension (vascular and parenchymal) 16; (3) toxemias of pregnancy 4; (4) pheochromocytoma (suspected) 1. The feature common to all these hypertensive patients was a diastolic blood pressure persistently above 90. Sixty-nine were receiving antihypertensive drugs at the time the test was performed. Forty-five were males and 39 were females, and they ranged in age from 14 to 4 years. Among the normotensive subjects, 46 were males and 50 were females, and they ranged in age from 18 to 72 years.

The amount of angiotensin II (Hypertensin-Ciba) injected was 0.1 γ diluted in

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0.1 c.c. of saline. This was the same amount used by the other authors with the exception of Hazelrig and associates,[4] who also employed a lower concentration of angiotensin (0.05 γ). An equal amount of pure saline was injected into the same area on the opposite arm. Disposable needles were used. Both angiotensin and saline were injected intradermally. Only fresh solutions of angiotensin were used. The solutions were kept refrigerated at 3 to 5°C. but were allowed to warm to room temperature before being injected. The site of injection was always the volar aspect of the forearm. Before the injection the skin was cleansed with alcohol and then allowed to dry. No untoward reactions were observed. No changes in blood pressure values were noted.

Results

In the normotensive group the average duration of blanching was 52 minutes, with a range between 15 and 140 minutes (S.D. = 23.5). The average value observed in the 31 healthy subjects was 51 minutes (S.D. = 24). The average value observed in the 65 patients who were normotensive but affected by some ailment not involving the cardiovascular or renal system was 53 minutes (S.D. = 18).

The average duration of blanching observed in the 84 hypertensive patients was 56 minutes, with a range of 20 to 130 minutes (S.D. = 20.6, $p > 0.2$, $p > 0.3$, and $p > 0.3$ respectively, when compared with average values obtained in the normotensive groups).

In 62 normotensive patients and in 58 hypertensive patients the blanching lasted for more than 30 minutes. This was maintained by Jablons[1,2] to be the "critical" point between normotensive and hypertensive subjects. The longest duration of blanching (140 minutes) was observed in a healthy young woman. The injection of saline produced a "blanching" in 10 subjects and a small red papule in 12 other subjects. Both these reactions were of limited intensity and fleeting in character. They lasted for a maximum of 15 minutes. The injection of angiotensin never produced a red papule. In 172 subjects the maximum intensity of blanching was observed within 10 minutes after the injection; in 8 patients the maximum intensity was observed within 15 minutes. There was no difference between hypertensive and normotensive subjects in the time required to reach the maximum intensity. No constant relationship was found between the intensity (area) of blanching observed at any given time and the type of hypertension. Finally, no substantial difference in response was observed between treated and untreated hypertensive subjects.

Discussion

The similar results obtained in normotensive and hypertensive patients confirm the negative findings already observed by Corcoran and associates[3] and by Hazelrig and associates. The intradermal angiotensin skin test in our experience was of no value in differentiating normal subjects from hypertensive patients or in differentiating among the various hypertensive patients. Furthermore, no relationship was found between the time of appearance and the intensity and duration of blanching and the type of hypertension.

In 13 of our normotensive patients who showed the presence of moderate to severe liver impairment, as demonstrated by changes in bilirubin levels, thymol turbidity, alkaline phosphatase, Bromsulphalein, SGOT, cephalin flocculation, and serum proteins (2 cases of fatal hepatic coma, 3 cases of infectious hepatitis, 2 cases of acute alcoholic hepatitis, 5 cases of Laennec's cirrhosis with ascites, and 1 case of biliary cirrhosis with ascites), the average time of blanching observed was 55 minutes (S.D. = 19). This was not statistically different from that observed in normal subjects or in hypertensive subjects ($p = 0.6$ and $p > 0.8$, respectively). Therefore, in light of our data, the results obtained by Mullane[5] in alcoholics with liver impairment also remain unexplained.

Since the presence of angiotensinases in the skin in significant amounts has never been proved,[3,4] to explain the positive result observed in hypertensive subjects by this mechanism[1,2] is only a matter of speculation. Furthermore, to postulate[5] an altered skin metabolism of angiotensin because of impaired liver metabolism of the same substance seems also to be a speculation, even if the existence of

cutaneous angiotensinases were proved Mullane on the basis of his observations in dogs with experimental ascites secondary to ligation of the common bile duct ad vanced also the hypothesis that a state of hyperaldosteronism may be present which affects the renin-angiotensin system. This hypothesis seems to be more interesting in view of recent studies which tend to demonstrate a definite relationship between the renin-angiotensin system and aldosterone.[7, 8]

In this regard it would be interesting to see whether in proved cases of hyperaldosteronism the life of angiotensin injected intradermally is actually prolonged In our 5 patients with liver cirrhosis and ascites in whom a secondary hyperaldosteronism could be expected to be present, no significant prolongation of the blanching was observed Unfortunately determinations of aldosterone were not available and therefore no conclusions could be drawn from this study

The negative results obtained with the intradermal administration of angiotensin are not necessarily in conflict with the findings of an increased reactivity to systemic angiotensin observed in most hypertensive patients[18-19] and of a decreased reactivity noted in patients with cirrhosis and ascites[7, 14, 1]

The discrepancy may be explained by the fact that intradermal angiotensin affects chiefly the precapillary sphincters, which at least in the skin may not be greatly involved in the hypertensive process. The vessels affected by intravenous or intra-arterial administration on the other hand, are proximal to the precapillary sphincters and include the arteriovenous anastomoses These vessels may be more or less reactive because of altered sodium content and abnormal electrolyte composition[1, 20] or because the angiotensin is taken up in abnormal quantities by an altered storage mechanism for vasoconstricting substances, such as norepinephrine[11, 4] The blood levels of endogenous angiotensin[7, 1] and the action of angiotensin and aldosterone on sodium metabolism seem to play an important role too[7, 7]

We may conclude by stating that the response to the intradermal injection of a diluted solution of angiotensin is a nonspecific reaction to a vasoconstricting substance It probably represents the local response of arterioles and precapillary sphincters to a vasopressor drug Therefore, the angiotensin skin test has no clinical application either in differentiating hypertensive from normotensive patients or in differentiating patients with liver impairment from normal individuals

Summary

The intradermal injection of 0.1 γ of angiotensin diluted in 0.1 c.c of saline failed to show any difference in response between normotensive and hypertensive individuals The average time of blanching was found to be statistically the same in both. Furthermore no constant correlation could be found between blanching and the type of hypertension Finally no significant variation was found between normal subjects and patients with moderate to severe liver impairment The conclusion was that the response to the intradermal injection of angiotensin probably represents a simple local reaction of arterioles and precapillary sphincters to a vasoconstricting substance

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Left axis deviation induced experimentally in a primate heart

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Electrocardiographic consequences of lacerations of the left side of the septum in the beating canine heart in situ were reported in an earlier paper.[1] Interruption of a major segment of the left bundle branch produced delay in arrival of the excitation process at epicardial points on that portion of the ventricular wall supplied by the severed conduction pathways. In varying degrees, anterior lesions were attended by slight shifts to the left of the mean electrical axis of QRS, whereas posterior lesions usually invoked reciprocal changes. Yet in no instance did an anterior septal laceration result in left shift beyond +30 degrees in the frontal plane.

This failure in the dog to duplicate the phenomenon of clinically significant left axis deviation as it occurs in man prompted us to undertake similar experiments in a primate (baboon). The results of these experiments on primates are herein reported and compared with earlier investigations on dogs.

Methods

Phencyclidine† (2 to 3 mg. per kilogram) was administered intramuscularly to each of 8 baboons, which were then further anesthetized as needed with intravenous pentobarbital (initially 10 to 15 mg. per kilogram). The chest was opened via a midsternal incision, and the pericardium was formed into a supporting sling. A helical copper wire electrode served to introduce a No. 1 black silk ligature first through the septum, thence back through the left ventricular cavity to the point of introduction. (For further description, see Reference 1.) Sawing back and forth on the ligature then produced the laceration. The position of the torso and limbs was carefully maintained throughout each experiment, at the end of which the extent of the lesion was determined by direct examination of the interior of the heart.

Electrocardiograms were recorded before and after production of each laceration. These consisted of standard and unipolar

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limb leads, right and left precordial leads V_1 and V_6, and an esophageal lead V so placed as to lie behind the main left ventricular mass. All records were made at a paper speed of 50 mm per second with an additional recording of approximately perpendicular Leads I aV$_F$ and V at 200 mm per second for timing purposes. Direct unipolar leads were taken at 200 mm per second from points on the epicardium by means of a soft saline-impregnated cotton tipped unipolar electrode. All tracings were recorded photographically on a Sanborn 550-M multichannel optical galvanometer system utilizing either 350-1600 or 350-3200 electrocardiograph preamplifiers presenting essentially infinite input impedance to a D C signal and a maximum loss of 30 per cent from 0 1 to 60 cycles per second





Fig 1 there Interior o Anterior and posterior ; posterior septal fibers development of left a Smallest hori Vertical stan dentally ur

Baboon No. 5 are t left and trocardiograms n block nd I ent 0 01 (20 mm./n

t top of picture apex at bottom Note the extensi lesion sparing fter (B) septal lacer tion, how QRS duration remained 0 06 sec /sec and 200 mm /sec paper speeds I V after lacer tion (B) w

Results

Remote and semidirect leads. Canine studies[1] had disclosed that no septal lesion or combination of septal lesions caused greater shift of axis than did a long laceration extending from a high basal anterior position toward but not including the posterior false cord and thence downward to the apex. In Fig. 1 is pictured a baboon heart in which such a laceration was produced. Marked leftward shift occurred in the mean frontal QRS axis.

The production of this kind of septal lesion was an accomplished aim in 7 of the 8 experiments on baboons, the results of which are summarized in Table I. As indicated therein, in animals No. 2 and 3, both small and judged to be of younger age than the rest, lesser axis shift occurred. In animal No. 4 (data omitted from the table) the depth of the lesion was such as to produce also a right bundle branch block. Each of the other 5 animals developed upon laceration greater axis shift than had been observed after similar lacerations in any one of the 32 canine experiments.

To study the effect of anatomic position on axis, observations made during canine studies were repeated in the experiments on baboons. Closing the operative wound in the dog and placing the torso in a left lateral position had produced no increase in axis shift to the left after anterior septal laceration. However, even in the unlacerated state, mechanical rotation of the canine heart in a counterclockwise direction, thus bringing the normally posterior mean QRS vector into a superior and lateral direction, produced left axis deviation. Corresponding mechanical counterclockwise rotation of the baboon heart in the unlacerated state also produced left axis deviation, whereas clockwise rotation after laceration, so bringing the abnormal superior and lateral mean QRS vector into a more posterior and inferior direction, returned the axis toward normal (Fig. 2).

Direct epicardial leads. Fig. 3 portrays the delay in arrival of excitation at selected epicardial points on the anterolateral free wall of the left ventricle after the septal laceration shown in Fig. 1. Lead V was derived from a point at which timing of intrinsic deflection increased from 36 to 58 msec., indicated on the figure as 22, which number defines in milliseconds the delay imposed by septal laceration. Similarly, other numbers designate increments of intrinsic deflection time found at each respective point. Changes in form of the Q wave

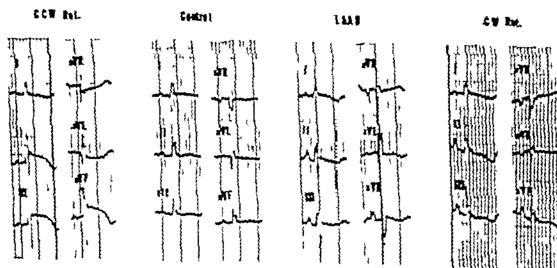


Fig. 2. The first electrocardiogram shows the effect of counterclockwise rotation in producing left axis deviation. The second tracing has the control record for comparison. After laceration ([illegible] left anterior arborization block), similar left axis deviation occurred in the unrotated state but was eliminated by clockwise rotation. (All illustrations were recorded from Baboon No. 6, Table I.) Paper speed [illegible] 50 mm./sec. with scale divisions as in Fig. 1.

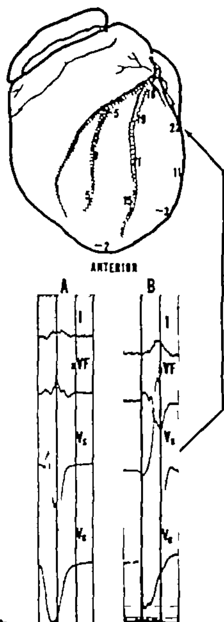


Fig 3 Same experiment as in Fig 1 Drawing of anterior aspect of heart showing distribution and degree of delay in arrival of excitation, as reflected in the timing of the intrinsic deflection in direct epicardial leads. At each epicardial point, the number shows the increment in milliseconds between intrinsic deflection time before laceration and that after laceration. A representative complex from a direct epicardial lead (V) over the most delayed recorded point (indicated by arrow) is presented in the lower half of the figure In *A* before production of the lesion intrinsic deflection time was 36 msec a *small R was followed by a deep S and only a minute* Q wave was present. In *B* after production of the lesion, intrinsic deflection time had increased to 58 msec (a delay of *22* msec—indicated by the number *22* on the drawing), R had become taller with corresponding reduction in S and a broader and slightly deeper Q wave was present (Table I Baboon No 5). Vertical standardization was 20 mm./mv for Leads I and aVF and 2 mm./mv for Leads V and V (unipolar lead from cavity of left ventricle).

and the increase in R/S ratio from 6/28 to 41/8 (in millimeters) also followed laceration These changes simulated precisely those encountered in comparable canine experiments (see Figs 4 and 6 and Table I of Reference 1)

The remarkable similarity between dog and baboon in the degree and distribution of delay in epicardial excitation contrasted sharply with the divergent results in these *same species in regard to the effect of septal* laceration on the mean frontal QRS axis. The search proceeded for some feature of ventricular excitation as manifested in *direct epicardial leads, which might account* for the species differences in the degree of shift of mean electrical axis as delineated in remote leads. The most satisfying product of this search was the identification of *certain differences* between *the form* of QRS complexes in epicardial leads from baboon heart on the one hand and those from dog heart on the other These differences will now be illustrated

Figs. 4 and 5 from a representative canine experiment are counterparts to Figs. 1 and 3 from a baboon experiment. Fig 6 facilitates the study of the QRS form in these same two experiments at specific epicardial points, which are indicated by the large black dots upon the respective heart sketches. Although the deflections pictured were traced from records in single canine and primate experiments, these deflections typify consistently recurring forms in multiple experiments on both dog and baboon. Fig 6,*A* depicts traces of complexes from a lead in the basal anteroseptal region of the left ventricle. Note that in the dog the control complex has an Rs form and in the baboon an rS Timing of intrinsic deflections is 38 and 42 milliseconds respectively after onset of QRS in a left cavity lead After production of the septal laceration the QRS assumes the form of a monophasic R wave in both dog and baboon and the intrinsic deflections occurred at 44 and 59 milliseconds, respectively

In Fig 6 *B* are tracings of ventricular complexes derived from a unipolar epicardial lead at a point midway between the base and apex and near the junction of the left posterior ventricular free wall with the septum Note that in the dog the control form of QRS is again an Rs deflection,

Table I. Summary of experiments

Baboon number	Weight (lbs.), Sex	*Frontal axis*		*Intrinsic delay (maximum in msec.)*	*R/S ratio*		*Q-wave increase*
		Before	*After*		*Before*	*After*	
1	27, M	+70	−70	25	1/10	13/11	Yes
2.	12, F	+70	+50	22	1/25	17/2	Yes
3.	9, F	+70	+40	18	7/21	29/6	No
5	41, M	+60	−60	22	6/28	41/8	Yes
6.	31, M	+70	−30	23	6/23	67/2	Yes
7	20, M	−10	−60	31	16/27	77/0	Yes
8	44, M	+70	0	30	36/6	61/11	No

Baboon No. 4 was omitted because of complicating right bundle branch block. Baboon No. 7 was of species hamadryas, whereas others were of species anubis that may or may not account for the horizontal frontal axis. Mean frontal QRS axes were estimated to the closest 10 degrees from tracings of conventional limb leads. R and S deflections were each measured in millimeters from the isoelectric base line. R/S ratios and Q-wave increases are presented for that epicardial point at which was observed the greatest increment in time of intrinsic deflection after septal laceration.

whereas in the baboon the form is again rS. Intrinsic deflection times are identical at 30 milliseconds. After production of the septal laceration the S wave widens in both dog and baboon complexes, but the ratio of R to S is not altered remarkably.

In Fig. 6 C are shown complexes from a lead at a point midway between the base and apex at an epicardial site overlying the region between the anterior and posterior papillary muscles. Note the greater similarity at the laterally disposed point, as contrasted with the anterior and posterior points, of control QRS complexes in dog and baboon with R waves dominating S waves in both species. However, the intrinsic deflection is 10 milliseconds later in the baboon than in the dog. After production of the septal laceration the timing of the intrinsic deflection was measured at 38 milliseconds in both the dog and the baboon and the S wave had widened and deepened to a greater degree in the baboon than in the dog.

Discussion

Data presented herein indicate that a lesion in the left anterior aspect of the ventricular septum which produced only slight axis shift in the dog produced marked left axis deviation in the baboon. This disparate behavior is at least superficially paradoxical since the distribution and degree of delay in arrival of excitation over the left anterior ventricular epicardium in the two species was essentially the same for a similar septal lesion. Identification and analysis of factors responsible for this difference is warranted for such insight as may be derived concerning the morphologic and electrophysiologic properties essential to the development of marked left axis deviation.

Two factors, our data suggest, are relatively unimportant. These are (1) electrocardiographic position of the heart (Wilson) and (2) thickness of the ventricular wall. Two other factors deserve careful appraisal. These are (3) the degree to which high-speed conduction pathways penetrate the ventricular myocardium and (4) species differences in the origin and distribution of primary fibers of the left bundle branch.

1. Electrocardiographic position of the heart (Wilson). Neither in the baboon nor in the dog, as seen in Figs. 1 and 4, was there clearly discernible horizontal or vertical electrocardiographic disposition of the heart prior to laceration. No close correspondence existed between QRS form in Leads V_1 and V_6 on the one hand and that in Leads aV_L and aV_F on the other. After laceration canine tracings remained essentially unchanged whereas primate tracings revealed a definite horizontal position (V_1 like aV_F and V_6 like aV_L). Since the point of departure in regard to electrocardiographic position was approximately the same in the dog and baboon, ascription of this factor of the marked left axis deviation



Fig 7 Photographs of left aspect of the septum in (*A*) calf (*B*) dog (iodine stained), and (*C*) baboon The left branch arises as a narrow band in the calf as a broader but still identifiable band which divides into anterior and posterior false cords in the dog and as columnae which diverge at wide angle from a high septal point in the baboon

gross morphology of the left bundle branch are illustrated in Fig 7

In the calf (Fig 7,*A*) the left bundle branches from the common bundle at an angle approaching 90 degrees. The left branch is a little wider than is the right and descends for 2 cm. or more on the upper left septum before dividing into major anterior and posterior divisions.

In the dog (Fig 7 *B*) the left branch again arises from the common bundle at an angle of approximately 90 degrees but its width is several times that of the right branch and approximates 1 cm Its principal divisions form the false cords which run free across the ventricular cavity to the anterior and posterior papillary muscles. A portion of its substance is continued into the mid-septal plexus, which extends well down toward the cardiac apex.

About the structure of the left branch in the baboon data are suggestive but as yet inconclusive In Fig 7 *C* is shown the upper left septum of a baboon heart from the present series. Note the wide angle formed by the columnae carneae which run from the upper mid-septum toward the junctions of the anterior and posterior portions of the septum with the ventricular free wall Disposition of these structures suggests that in the baboon as in the human heart[2-4] the left branch is formed either as a broad ribbon or as multiple discrete fascicles arising along the length of the common bundle. Additionally note absence of false cords as free running structures spanning the ventricular cavity *

Items 3 and 4 of this discussion imply then *two differences in the nature of the* excitation process between baboon and canine hearts (a) The rapidly conducting elements extend further from endocardium toward epicardium in the baboon than in the dog heart. As a result the electrical endocardium is correspondingly thicker in the baboon and the magnitude of tangential forces developed during excitation is correspondingly greater (b) By virtue of the broad origin and wide angle of spread of left bundle branch fibers across the upper septum in the baboon these tangential forces in the intact heart envelop the left ventricular free wall from its septal attachments anteriorly and posteriorly and con

*Comparison of canine and baboon hearts in the present study suggests also that at least the posterior margin of the left branch arises more posteriorly in the baboon than in the dog. In Fig 7 this distinction between the hearts of the two species is not clear but examination of all specimens in this study revealed that structural elements believed to constitute the left bundle branch are first apparent near the sulcus between the right and posterior aortic valve cusps in the dog, and between the posterior and left aortic valve cusps in the baboon.

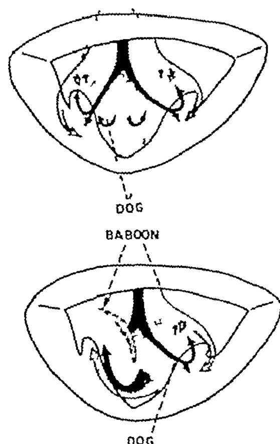


Fig. 8. Schematic drawing of interior of the left ventricle before and after anterior septal laceration. Bold shading represents proposed pathways in the dog; light shading, in the baboon. For description see text.

verge toward the lateral margin of that free wall. Such a conception of ventricular excitation is supported by the rS form of epicardial complexes from anteroseptal points (Fig. 6,A), posteroseptal points (Fig. 6,B) and the Rs form of epicardial complexes from a point on the lateral wall (Fig. 6,C). After septal laceration in the baboon, these tangential forces spread from the posteroseptal into the apicolateral left ventricular wall and thence into that portion of the basal anterolateral wall to which the rami of the left branch have been severed.

The elements of this hypothesis, proposed to account for the greater axis shift produced by anterior septal laceration in the baboon than in the canine heart, are presented in schematic form in Fig. 8.

Summary

Production of a septal laceration which interrupts the anterior rami of the left bundle branch in the baboon heart is attended by changes in the spread of excitation into the anterior free wall of the left ventricle. These changes are expressed in the following electrocardiographic alterations: (a) Delay of arrival of excitation at the epicardium of the involved area. Degree of delay ranged from zero at boundaries of the involved area to 20 milliseconds or more at central points. (b) Shift to the left of mean electrical axis in the frontal plane to a degree sufficient to satisfy criteria for clinically significant left axis deviation in the human being.

These results are compared with those derived from similar and previously reported studies on dogs wherein lesser degrees of axis shift were encountered. Species differences in results are believed to depend primarily on differences in the mode of spread of excitation into the ventricular myocardium. These latter differences in turn, may derive from species peculiarities in the distribution of the major divisions of the left bundle branch and in the degree to which terminal ramifications of the rapid conduction pathways penetrate the free wall of the left ventricle.

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Case reports

Dextrocardia complicated by hypertension and myocardial infarction

A case report

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Only a few cases of myocardial infarction in people with dextrocardia have been reported in the medical literature.[1-8] The first report was that of Crawford and Warren[1] in 1938, and since then there has been a total of 7 cases reported in the literature, the last one being the case of Jacoby and Jacobson[8] in 1963.

Uncomplicated dextrocardia is not a common disease. Its incidence has been reported to vary from 1 per 6,200 to 1 per 35,500, with an average of 1 per 9,300. The presence of myocardial infarction and hypertension in association with this entity is even a greater rarity, and for this reason the following case is being reported.

Case report

A 70-year-old white woman was admitted to the University District Hospital on Aug. 5, 1961. Pertinent history dated back to 20 years previously, when she had been found to have hypertension, for which she received oral medications intermittently.

For the 10 years preceding the hospitalization she had been having progressive shortness of breath on exertion and when lying down flat. She also complained of occasional swelling of the legs. In 1954 she was found to have diabetes mellitus, which was kept under control with 20 units of NPH insulin daily.

Since 1956, she had had episodes of anterior chest pain, pressing in quality, accompanied by a feeling of tiredness or heaviness in the right arm, the right side of the chest wall, and the right jaw. These episodes occurred more often on emotional upset or exertion, but also at rest. The pain would last from a few minutes to 2 hours and was apparently relieved by bed rest and home remedies. On the day of admission the patient had a similar episode of chest pain, but this time it lasted 6 hours. The physical examination revealed a well-developed, well-nourished, alert and cooperative woman who was in no acute distress. She had a blood pressure of 180-210/110 mm. Hg, a regular pulse of 80 per minute, and respirations of 20 per minute. The fundi were not visualized because of miosis of the pupils. There was prominent kyphoscoliosis. The chest wall was hyperresonant all over. The diaphragm was low by percussion. The respiratory excursion was poor bilaterally. Rhonchi were heard on auscultation, but there were no râles. Examination of the heart revealed that the point of maximal impulse was in the fifth intercostal space just lateral to the right mid-clavicular line. The heart sounds were distant and the rhythm was regular. No murmurs or thrills were found. There was no hepatosplenomegaly, edema, or cyanosis. The peripheral pulses were adequate in all extremities.

The serum glutamic oxaloacetic transaminase was 70 units, and the serum glutamic pyruvic transaminase was 41 units on the day of admission. The

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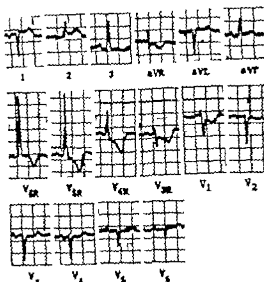


Fig. 1. The mirror image complex in Lead I and the tracings in Leads aVR and aVL are compatible with dextrocardia. Inversion of the T waves is noted from Lead V R to Lead V . Some downward displacement of the S-T segment is present in Leads V R, V R, and V .



Fig. 2. X-ray film of the chest reveals the presence of dextrocardia.

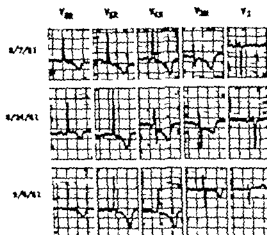


Fig. 3. Serial precordial leads on the right side reveal inversion of the T waves. On the tracing of Aug. 24, 1961, there is a downward displacement of the S-T segment in Leads V R and V R. The T wave in Lead V was upright by Sept. 4, 1961.

white blood cell count was 10,500 per cubic millimeter. Multiple determinations of transaminase and lactic dehydrogenase for many days thereafter were normal. The electrocardiogram revealed dextrocardia and other changes (Fig. 1). The x-ray films of the chest (Fig. 2) confirmed the diagnosis of dextrocardia and situs inversus. Complete bed rest was recommended but the patient did not follow instructions.

On August 24 the patient experienced another episode of severe anterior chest pain that radiated to the right arm. The electrocardiogram was taken, and the precordial leads on the right side are shown in Fig. 3. Anticoagulation with Coumadin was started that day. The transaminases and lactic acid dehydrogenase remained normal. Another episode of pain in the right side of the chest, accompanied by weakness of the right arm and dizziness, occurred on September 16. The lactic dehydrogenase rose to 930 units and the serum oxaloacetic transaminase to 300 units, but the electrocardiogram remained the same as that of Sept. 4, 1961. Salicylates and Demerol were used as needed. Anticoagulation with Coumadin was continued, and the rest of the hospital stay was uneventful. The diabetes was easily controlled with diet and NPH insulin.

On Nov. 11, 1961, she was discharged improved. The patient failed to return to follow-up and when she was recalled for a checkup, we were informed that she had died at home in 1963.

Discussion

Only 7 cases of dextrocardia with myocardial infarction have been reported in the medical literature prior to this report. Table I illustrates the salient features in those cases and in the case that we are reporting here. Five patients were males and 2 were females. Our patient was a woman. The youngest woman was 56 years old, whereas 3 of the 5 men were younger than that. The mean age of the

Table I Patients with dextrocardia and myocardial infarction

Patients	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*	*Case 7*	*Our case*
Age (yr)	43	58	37	56	53	73	89	70
Sex	M	M	M	F	M	M	F	F
Site of pain and radiation	Substernal radiating to both shoulders	Right of the sternum also numbness in right	Pain inferior to the right scapula		Right anterior chest radiation to right shoulder and arm	Substernal radiating to right arm	Right upper abdomen not referred	Right side of chest; in right arm
Nature of pain	Moderate, twisting	Constricting	Sudden		Crushing	Severe sudden	Like a gas pressure	Heaviness, pressing, oppressive
Situs inversus	+	+	+			+	+	+
Hypertension	No	No	No	Yes	Yes	No	No	Yes

Superscript numbers indicate the reference

men was 52 8 and that of the women was 71 7 years. Hypertension had been present in 2 of the 7 reported cases. Our patient is the third patient reported with dextrocardia *hypertension and myocardial infarction*

Of the total of 8 patients with dextrocardia and myocardial infarction 6 had pain in the structures on the right side of the body one had pain in both shoulders, and in one the radiation of pain was not reported

Anginal pain in the normally implanted heart is usually felt substernally and often radiates to somatic structures such as the arms and neck, which are innervated by the same segment of the nervous system as the side of the heart in which the pain has its origin The radiation may be to both sides but most often is confined to the left. On rare occasions it radiates mainly to the right side.

The heart is a midline structure which is embryologically supplied by nerves from both sides of the body It appears on embryological grounds, that the interatrial septum left ventricle the commencement of the aorta, the oblique vein of Marshall and the coronary sinus are left-sided structures. The remainder of the right atrium the right ventricle, and the origin of the pulmonary artery are right-sided structures. The interventricular septum is a midline structure The right-sided and *left-sided structures are supplied by nerves* from the corresponding side of the nervous system It follows that frequently pain on the right side means dysfunction of the right chambers and pain on the left side of the left chambers and interatrial septum [9]

In cases of coronary thrombosis or angina occurring in subjects with a heart normally to the left side of the body the vascular changes or infarction developed will chiefly involve the left ventricle and atrium although sometimes will also include the right The pain is usually referred either partially or entirely to the left side and is not frequently restricted to the right side. In cases of isolated dextrocardia a coronary thrombosis would chiefly involve the ventricular mass which is anatomically located on the right side of the body and the pain apparently would be transmitted by *the nerves on the right* side with a consequent referral of pain to the somatic structures on the right side

The pain although radiating to the right side is similar in nature to that of the

usual case of myocardial infarction and the regular means of diagnosis, such as electrocardiograms, enzyme studies, and acute phase reactants are of help when obtained. Electrocardiograms with inverted leads are most helpful when used.

Summary

A case of myocardial infarction and hypertension in a woman with congenital dextrocardia is presented. A review is made of 7 other cases taken from the medical literature. An analysis of the clinical features of this uncommon entity is included.

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Unusual form of digitalis-induced double atrial tachycardia

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It is well recognized that digitalis may produce various cardiac arrhythmias due to alteration of either impulse formation or conduction in the heart. The present paper describes a very unusual form of double atrial tachycardia as a manifestation of digitalis toxicity. The related literature is reviewed.

Case report

A 67-year-old man was admitted to the hospital complaining of dyspnea of 1-week duration. He had been known to have had recurrent episodes of congestive heart failure for 2 to 4 years due to arteriosclerotic heart disease. His therapy before admission consisted of digoxin, .25 mg., and hydrochlorothiazide, 50 mg. daily.

The significant findings on physical examination were: blood pressure of 150/95 mm. Hg, irregular tachycardia at 110 beats per minute, moderate left ventricular hypertrophy, and bilateral basal pulmonary râles. X-ray examination of the chest showed moderate left ventricular hypertrophy with pulmonary congestion. The electrocardiogram taken immediately after admission revealed an unusual atrial tachycardia from two different foci, with intermittent 2:1 atrioventricular block (Fig. 1). The blood chemistry was normal, except for a serum potassium of 3.2 mEq. per liter. The digitalis was discontinued and 40 mEq. of potassium was administered intravenously. Twelve hours later when an electrocardiogram was obtained, the rhythm was of sinus origin.

Analysis of electrocardiogram. Fig. 1 exhibits a double atrial tachycardia with varying degrees of atrioventricular block. There are two different P waves with different P-P cycles. The ectopic pacemaker with the longer P-P cycle (Type A) produces atrial tachycardia with a rate of 140 per minute and 1:1 atrioventricular conduction with first-degree atrioventricular block (P-R interval is 0.22 second). The P-P cycle in this group is 0.44 second. The other atrial pacemaker (Type B) produces a faster rate of 175/minute with 2:1 atrioventricular block. The P-P cycle *in this type* is 0.34 second. The P vector is oriented inferiorly, posteriorly, and to the left in Type A, whereas in Type B it is oriented inferiorly, anteriorly, and to the right (interpreted from the complete tracing of this patient). It can be assumed that the ectopic focus is located in the right atrium in Type A and in the left atrium in Type B tachycardia. It is interesting to note that there are frequent atrial fusion beats between the two atrial impulses (labeled *FB*). The diagnosis of atrial dissociation cannot be made in this tracing because both atrial pacemakers control the ventricle, whereas in atrial dissociation, only one pacemaker is in control of the ventricle.[illegible]

Discussion

The diagnosis of recurrent congestive heart failure was made in this patient. However, it was difficult to judge whether it was a manifestation of digitalis intoxication clinically. Digitalis intoxication was

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Fig. 1. Double atrial tachycardia. Downward arrows indicate longer P-P cycle (0.44 second) and this tachycardia (Type A) shows 1:1 atrioventricular conduction with first-degree atrioventricular block (P-R interval 0.22 second). Upward arrows indicate shorter P-P cycle (0.34 second) and this tachycardia (Type B) shows 2:1 second-degree atrioventricular block. Atrial rate is 140/minute in Type A and 175/minute in Type B. Note frequent atrial fusion beats (*FB*).

suspected because he was an elderly patient who had been taking diuretics, and paroxysmal atrial tachycardia with atrioventricular block is known to be associated with such a situation.

Digitalis has two distinct actions on the heart, direct and indirect; both can influence cardiac excitability, conductivity, and rhythmicity. The direct action is on the myocardium and produces myocardial depression. The indirect action produces vagal stimulation. Both actions have depressive effects on atrioventricular conductivity so that digitalis may produce various degrees of atrioventricular conduction disturbance. The appearance of atrioventricular block due to digitalis was first described by MacKenzie[3] and Lewis. By the indirect action (vagal stimulating action) of digitalis the refractory period of atrial musculature can be markedly shortened. Thus, increased conductivity in the atrial muscle can produce various rapid atrial arrhythmias. On the other hand, digitalis has a depressive action directly on the atrial myocardium. The end result of digitalis effect on the atrial muscle depends on which action is dominant. The combination of the depressive effect on the atrioventricular conduction and the shortening effect on the refractory period result in rapid atrial arrhythmia with varying degrees of atrioventricular block.

The most common form of digitalis-induced atrial arrhythmia is paroxysmal atrial tachycardia with block,[5-10] although atrial flutter[11,12] and atrial fibrillation due to digitalis intoxication have been reported. The occurrence of double atrial tachycardia due to digitalis toxicity has not previously been reported in so far as we can ascertain. Digitalis-induced double supraventricular tachycardia consisting of atrial tachycardia and atrioventricular nodal tachycardia or double atrioventricular nodal tachycardia producing atrioventricular dissociation has been observed.[illegible] This probably occurs since digitalis may accelerate the atrioventricular nodal pacemaker.[illegible]

It is well documented that digitalis intoxication is frequently encountered in hypokalemia.[illegible] Hypokalemia alone can cause cardiac arrhythmias[illegible] as well as accelerate those induced by digitalis. It is also known that the myocardium may lose potassium because of heart failure itself, thus predisposing to digitalis intoxication.[illegible] In elderly patients such as herein reported who are being treated for congestive heart failure with digitalis and diuretics, digitalis intoxication may be easily produced since such patients have poor myocardial reserve and are especially sensitive to digitalis.[illegible] The sudden appearance of rapid heart action, particularly paroxysmal atrial tachycardia during digitaliza

tion in elderly individuals should make one suspicious of digitalis toxicity rather than the need for increased digitalis

Summary

An instance of digitalis-induced double atrial tachycardia with atrioventricular block has been described To our knowledge it is the first such arrhythmia reported

One ectopic focus was assumed to be located in the right atrium (type A) and the other in the left atrium (type B)

The influence of digitalis and hypokalemia in relation to such cardiac arrhythmia has been discussed

The necessity of early recognition of digitalis intoxication in elderly patients who develop supraventricular tachycardia particularly paroxysmal atrial tachycardia during digitalization has been emphasized

This patient was studied while Dr Chung was a Fellow in Cardiology at Barnes Hospital and Washington University School of Medicine, St. Louis, Mo. The greatest appreciation is expressed to Dr Edward Massie Director of the Heart Station at Barnes Hospital, for giving consent for this material to be presented.

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Unusually tall and narrow U waves simulating hyperkalemic T waves

Report of 2 cases of hypochloremic alkalosis with hypokalemia

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In the literature on U waves in hypokalemia,[1-4] no reference could be found to the maximum height of the U waves, or their narrowness, except for the following statement by Lepeschkin: "In pronounced hypopotassemia the U waves may become tall and pointed so that they may be mistaken for T waves . . . ." In the following two cases of profound alkalosis with hypopotassemia, such an extreme degree of peaking and tallness was observed over some precordial leads as to justify reporting them, particularly because of the partial simulation of a hyperkalemic pattern thus presented.

Case reports

Case 1. L.A., a 30-year-old man, was admitted to hospital on Feb. 1, 1963, with the complaint of abdominal pain of 3 years' duration and vomiting of 3 months' duration. A diagnosis of pyloric stenosis was made and gastrojejunostomy was performed on Feb. 7, 1963. From February 7 to February 16, he received an unspecified amount of parenteral fluids, consisting, on the average, of 3½ liter each of glucose and glucose saline. On February 16, he complained of severe vomiting which persisted for 10 days. During this period he was given about 2 liters of potassium-free parenteral fluids, including 5 per cent glucose and 5 per cent glucose saline, and the gastric contents were intermittently aspirated.

On examination at 10.30 A.M. on February 27, when I was first consulted, the patient was found to be semiconscious, boisterous, and moderately dehydrated, with a pulse rate of 78 per minute and respirations of 15 per minute and shallow. He was passing urine involuntarily. The blood pressure was 100/80 mm.Hg. Trousseau's sign (for latent tetany) was strongly positive in half a minute. ECG-1 (Fig. 1) was taken at 11.30 A.M. on the same day with blood control. Hypokalemia with hypochloremic alkalosis was suspected from the clinical circumstances and the ECG, and parenteral potassium therapy was begun. The details of parenteral therapy, serum electrolyte values, and the timing of subsequent electrocardiograms are shown in Table I. He continued to be semiconscious until February 28 at 6 P.M., when he began to respond to pinprick. The Trousseau sign became negative by 4 P.M. on February 28. His blood pressure ranged from 100 to 130 mm.Hg systolic and 80 to 90 mm.Hg diastolic until February 28, and subsequently was 100-110/70-80 mm.Hg. He was passing urine involuntarily during this period. Gastric aspiration was carried on intermittently until March 3, and averaged about 1 or 2 liters per minute. On March 2 he was still drowsy, but could speak coherently for the first time. By March 3 he became fully conscious. Aspiration was stopped, and oral fluids were supplemented. He was discharged in good general condition on March 13, 1963.

Case 2. A.B., an emaciated elderly woman, was admitted to hospital on Nov. 29, 1962, with the complaint of vomiting of 3 months' duration. A diagnosis of pyloric obstruction due to carcinoma of the stomach was made. Over the next 3 days she received an unspecified amount of parenteral fluid (about 1½ to 2 liters of 5 per cent glucose saline per day). On Jan. 1, 1963, when I was consulted, the patient was found to be in extreme semiconscious, and in shock. There were coarse twitchings of the limbs and mouth and rigidity of the neck. Trousseau's sign was strongly positive

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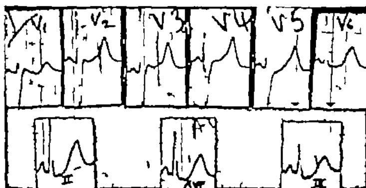


Fig 1 Shows Leads V_1–V_6, II, AVF and III of ECG-1 of Case 1 dated Feb 27 1963 11.30 A.M. See Table I and text for comment

Table I Case 1 Parenteral therapy ECG timing and serum electrolyte values

Date and time	*Details of parenteral therapy*	*ECG*	*Serum electrolytes (mEq/L.)*
Feb 27 1963			
11 30 A.M.	KCl, 100 mEq in 2 liters of 5 per cent glucose saline	*A* (Fig 1)	K 2 6 Na 130 Ca 5 Cl 50
9 30 P.M.	——	*B* (Fig 2a)	
	20 c.c. of 10 per cent solution of calcium gluconate given over 3 min. until 9.53 P.M.		
9.55 P.M.	——	*C* (Fig 2a)	
10.00 P.M.	——	——	K 3 3 Cl 50
	KCl, 62 mEq in ½ liter of 5 per cent glucose solution by rapid drip, 100 to 200 drops per minute given between 10 and 11 P.M.		
10.30 P.M.	——	*D* (Fig 2a)	
Feb 28 1963			
00 45 A.M.	KCl, 100 mEq in 2 liters of 5 per cent glucose saline		K 4 0 Cl 55
March 1 1963			
11:00 A.M.	KCl 50 mEq in 1 liter of 5 per cent glucose saline	*E* (Fig 2a)	
7:00 P.M.	KCl, 100 mEq in 2 liters of 5 per cent glucose saline	*F* (Fig 2b)	
March 2 1963	50 mEq of KCl in 2 liters of parenteral fluid		
... 1963			

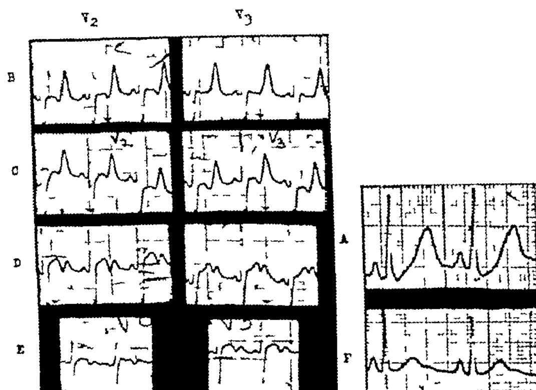


Fig. 2a (*left*). Shows Leads V and V of ECGs-*B* C,*D* and *E* of Case 1 See Table I and text for comment
Fig. 2b (*right*). Show Lead II of ECGs-*A* and *F* of Case 1 See Table I and text for comment.

The pulse rate was 96 per minute, the blood pressure was 70/ mm Hg and the respirations were 20 per minute and shallow. ECG-*A* (Fig. 3) was taken at 4 P.M. After 1 pint of 5 per cent glucose saline the blood pressure rose to 130/100 mm. Hg. She received 1 more liter of 5 per cent glucose saline by 9 45 P.M. when ECG-*B* (Fig. 3) was taken. By this time she had regained consciousness and could protrude the tongue when instructed to do so. ECG-*C* (Fig. 3) was taken at 9.50 P.M. 2 minutes after 20 c.c. of 10 per cent solution of calcium gluconate had been given intravenously over a period of 2 minutes. Over the next 12 hours she received 3 Gm. of KCl in liter of glucose saline and ECG-*D* (Fig. 3) was repeated on Dec. 2, 1963 at 3 P.M. On December 3, she received 4 Gm. of KCl in 1½ liter of glucose saline. Subsequently she received potassium orally but electrocardiographic appearances were not restored to normal, because of inadequate therapy and continued vomiting. She was discharged against advice on Dec. 30, 196_.

The electrocardiographic timing and determinations of serum electrolytes in this patient are given in Table II.

Comment

The clinical circumstances detailed in the two cases and the extremely low serum chloride values, may together justify a diagnosis of profound alkalosis although pH and alkali reserve could not be estimated.

In Case 1 the appearances in the limb leads in the initial ECG (*A* Fig. 1) are suggestive of severe hypokalemia, with a sagging S-T segment and tall undifferentiated repolarization waves (II, III, AVL, and AVF) and a moderate increase in the width and amplitude of the QRS complex and in the height of the P wave and length of the P-R interval. The latter changes (in the QRS complex, P wave, and P-R interval) are features of hypokalemia well documented in the rabbit[4] and in the dog but rarely recorded in man.[2,3]

In the chest leads of the same ECG however, the repolarization waves appear to be tall and rather sharp, following a sagging S-T segment. In spite of 8 Gm. of KCl over 10 hours the ECG appearances in *B* did not improve appreciably except in the correction of the S-T depression.

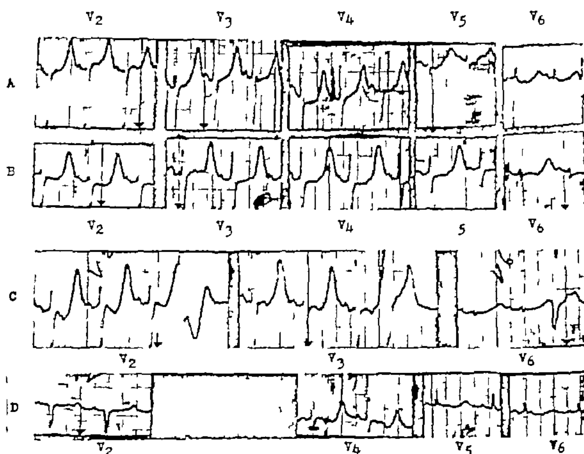


Fig 3 Shows Leads V2–V6 of ECGs A, B, C, D of Case 2. See Table II and text for comment.

Table II Case 2 Serum electrolyte values and ECG timing on various dates

Date and time	ECG (Fig 3)	K (mEq per liter)	Na (mEq per liter)	Cl (mEq per liter)	Ca (mEq per liter)	Total proteins (Gm. %)
Dec 1 1962						
4.30 P.M.	A	3.0	130	56	4.0	7.1
9.30 P.M.	B	2.7	144	52	3.2	6.5
9.50 P.M.	C	Not determined				
Dec. 2 1962						
3.00 P.M.	D	Not determined				
Dec 3 1962						
3.00 P.M.	—	4.2	140	72	5.0	—

At 9.30 P.M. the repolarization waves in Leads V_2 and V_3 (ECG-*B*, Fig. 2*a*) were actually taller and narrower than initially and not unlike the hyperkalemic T waves for which in fact they were mistaken by several observers. However, that these tall waves were wholly or almost entirely due to the U waves is shown by the following: (1) After injection of 20 c.c. of calcium gluconate (10 per cent solution) the distance from Q to the apex of the repolarization wave was practically unaltered and a small T wave was seen to emerge proximally. (2) Augmented potassium therapy by rapid drip (100 to 200 drops) of a 1 per cent solution of KCl caused the tall repolarization wave to be dwarfed and produced an elevation proximally corresponding to the T wave, thus proving even more clearly that the former was the U wave.

The electrocardiographic findings in the second case are essentially similar to those in Case 1. The repolarization waves became taller in ECG-*B* of Fig. 3 after 1½ liters of glucose saline which had lowered the serum potassium still further (Table II). The low serum calcium in this case would be expected to cause Q-T prolongation with fusion of T and U waves, and the T waves thus theoretically contribute to the tall T+U waves. The absence of any shortening of Q-aRP after injection of calcium gluconate solution and the emergence of a small negative T wave proximally suggest that the tall repolarization wave is formed mainly by the U wave in this case also.

In these two cases it is difficult to understand the cause for the unusual shape of the U waves, which by their resemblance to peaked T waves are apt to discourage the clinician from the use of parenteral potassium therapy exactly when it is most needed. Although the increased height of these waves is probably partly a reflection of the general increase in amplitude of all the complexes, the profound alkalosis may possibly have aggravated the effect of the hypokalemia.

Summary

Two cases of probably profound hypochloremic alkalosis with hypokalemia, both in semiconscious patients, are reported showing ECG changes of hypokalemia with unusually tall and narrow repolarization waves, in Precordial Leads V and V_3 in particular, formed mainly or wholly by the U waves and simulating hyperkalemic T waves.

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Review

Current status, unsolved problems, and future directions in congestive heart failure research

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One of the greatest achievements in the treatment of chronic congestive heart failure was the description of the use of foxglove by William Withering in 1786. Thus Withering's original observation must have been made at about the same time that the teaching of medicine was begun at the University of Pennsylvania. Hence it is especially appropriate to review our present standing in regard to this important and fascinating syndrome at this time of observance of the birth of the medical school in the United States of America.

Definition

In 1933 Sir Thomas Lewis[13] stated: "There is but one meaning to the term cardiac failure—it signifies inability of the heart to discharge its content adequately, and this failure culminates in manifestations with which we are all familiar, namely, dilatation of the heart, general venous congestion and dropsy. In the progress of failure these phenomena are late and they mean that the heart has failed in such degree that it has no longer the capacity to do the work required of it while the body is at rest. In much earlier phases of cardiac failure the underlying defect shows itself in a lack of reserve by means of the cardinal symptom breathlessness on effort."

The New York Heart Association's nomenclature for cardiac diagnosis[16] describes rather than defines heart failure. "Heart failure," it is stated, "occurs when the heart fails to circulate the optimal amount of blood required by the body. In cardiac insufficiency the cardiac output is always less than required. There is an inadequate emptying of the cardiac chambers, increased diastolic pressure therein and a greater than normal deoxygenation of the blood. . . . The failure of the ventricles to circulate the required volume of blood leads to congestion on the venous side of the vascular tree, either pulmonary or systemic or both (backward failure, congestive failure) and to inadequate blood flow on the arterial side (forward failure) with resulting alterations in the functions of the organs. The symptoms and signs of cardiac insufficiency depend upon which ventricle fails primarily and the degree and duration of its failure. Dyspnoea

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fatigue and cyanosis are the cardinal symptoms.

In 1963 Guyton[11] suggested the definition of cardiac failure "Both the words heart and failure are quite explicit, therefore the terms heart failure should mean very simply failure of the heart to pump blood as well as it does normally."

Many attempts have also been made to define in physiologic terms what the failure of the central pump means. Usually only some mechanisms by which the heart is believed to be able to continue to supply enough blood flow to the organism have been described. The point at which the pump is really failing and at which these mechanisms cannot guarantee the peripheral blood flow has never been defined in these terms. Dilatation of the heart chambers, an increase in filling pressure (by itself or in relation to the work done by the ventricle) a decrease in stroke volume, and an increase in heart rate are all such events wherein a fleeting development can be seen from the normal to the failing state without any clear-cut border line between the changes typical for compensated heart disease and those typical for decompensated heart disease.

All the examples cited obviously escape the real difficulty by oversimplification of a most complicated situation. This has not helped to clarify the events leading to the fully developed picture of congestive failure.

Nor has it been possible to demonstrate any typical derangement of the myocardial metabolism in failure although much research has been devoted to this question[3, 4]. It is highly probable that the dilatation of the ventricular cavities seen in heart disease imposes on the myocardium an uneconomical way of working as described by the Laplace formula. This would imply that the production of energy by the failing heart is normal but that the mechanical utilization of this energy is impaired. The search for a specific metabolic disturbance of the myocardium in failure carries the risk that the changes typical for some special myocardial disease leading to failure may be found rather that what is typical for the failing myocardium. More rigid criteria and adequate controls should be applied to this question.

Cardiac failure is thus a *clinical syndrome* that is observed in patients with heart disease and sometimes in patients with those metabolic disorders that exert a great demand on the central pump in the circulatory system. It is not without importance that cardiac failure is a clinical entity. Many obscure findings and points of disagreement between different schools of thought are basically due to overlooking this fact. Even if some mechanisms can be disclosed in the laboratory preparation, the clinical picture of a severely ill cardiac patient in chronic congestive failure in all of its varieties has not been fully reproduced in the laboratory animal and can thus be neither defined nor studied in the animal.

The attempts to define heart failure in physiologic terms have been unsuccessful. There does not seem to be any better physiologic generalization about cardiac failure than that expressed by Dickinson Richards[17] in 1947: "Heart failure seems to be more characterized by a disturbance of pressures than of flow."

Total blood flow

Cardiac output is usually low when a patient exhibits the typical signs of cardiac failure. The total blood flow, however, may be high in what has been called *high output failure*. That low output by itself does not necessarily mean cardiac failure is also clear from studies of hypokinetic states. The frequent discussion of the magnitude of the cardiac output in congestive failure and its changes when compensation is restored obscures the importance of the peripheral distribution of the blood flow. The large arteriovenous oxygen difference seen concomitant with low cardiac output in failure is partly due to a redistribution of blood flow from the renal, cutaneous, and hepatic circuits wherein oxygen consumption is relatively low. Thus this is similar to the flow pattern in normal subjects during exercise. The cardiac reserve is then so limited that even at rest the organism has mobilized resources originally designed to be used during exercise or other physical stresses.

Improvement of cardiac force when failure is receding may lead either to a better distribution of blood flow or to a better

perfusion of all organs or to both. The occurrence of clinical improvement without change in cardiac output may signify an important improvement in the peripheral distribution of blood flow, which often is obscured by the multitude of events occurring simultaneously. This was again demonstrated recently by Rader and her co-workers after treatment with mercurial diuretics when the cardiac output was unaltered but the oxygen content of the mixed venous blood increased.[77]

Total blood volume

One of the features connected with the development of congestive failure is an increase in blood volume.[78] The recent findings by Bojs and Conn[4] in dogs with spontaneous heart failure indicate that a marked increase may occur rapidly. However, there does not seem to be such an increase in blood volume in all cases of congestive failure. Some patients may even regain compensation concomitant with an increase in both red cell and plasma volume.[79] It is quite conceivable that venous constriction may elevate the venous pressure with a decrease in total blood volume and thus present all the classic findings of congestive failure. How much of the total intravascular volume—and especially when it is only moderately increased—may be found in the cavities of a dilated heart has never been studied sufficiently to give an unequivocal answer to whether and to what extent the peripheral blood volume is increased in failure. The important mechanisms regulating the total blood volume in man are as yet incompletely understood. Without a thorough knowledge of the normal rules for the maintenance of the blood volume within narrow limits it is impossible to know why and how it is altered when the circulation fails. It is also possible that our concept of a fixed intravascular volume is too crude to comply with the existing sensitive circulatory dynamics. Gregersen recently stated: "It is evident that measurement of the true total blood volume is still a relatively new development and it is entirely possible that greater precision in methods will be needed to study small changes in volume that are significant in regulatory mechanisms. If so, this would not be the first time that the receptor and feed-back mechanisms in the body were more sensitive than the methods of the experimenters."

Peripheral circulation

Starling called attention to the importance of a hemodynamic balance in the capillaries for the proper exchange of fluid between the intravascular and extravascular spaces. Recently the control of this important part of the vascular bed by the nervous system has been elucidated. Folkow and his co-workers have studied extensively the influence of the autonomic nervous system on the functions of the peripheral venous and arterial segments and analyzed the importance of the resistance and capacitance vessels for the function of the capillaries.[7,16,17] They demonstrated that the relationship between precapillary and postcapillary resistance is of decisive importance for the flow of blood through the capillaries, for the filtration surface of the capillary membrane, and for the shift of fluid between the intravascular and extravascular compartments.

So far, this regulatory mechanism was studied only in instances of sudden hemodynamic change due to loss of blood or after specific nerve or brain stimuli. The close association between these aspects of capillary function and the production of edema makes necessary the extension of this approach to study also the failure of the central pump. It is quite possible that nervous reflexes elicited from the heart or great vessels, for example, through a decrease in stroke volume, may influence the balance between the precapillary and postcapillary resistances and initiate the production of edema. The same reflexes may also take part in the increased venous tone in congestive failure.

Folkow and Mellander[7] in a recent review of their findings, warned however against too much theorizing at our present stage of knowledge: "Obviously hypotheses in this complex field run the risk of being invoked too early and more experimental work is badly needed before more definite statements can be made."

Similarly, Lysle Peterson[80] recently discussed the regulation of the state of the arterial wall and the many feed-back

systems that operate in determining the vascular resistance in arterial hypertension. Also in heart disease the vascular resistance, both generally and in some circumscribed vascular beds, may be increased. In congestive heart failure the resistance to flow is increased in many ways similar to that found in uncomplicated arterial hypertension and evidence has been presented which indicates similar mechanisms in these two syndromes.[1,2,3,4]

Pulmonary circulation

In clinical studies of heart failure the pulmonary circulation has attracted considerable interest while in animals the congestion of the systemic circulation, the venous return to the right side of the heart, and the systemic venous pressure have been studied more thoroughly. The recent studies by West[29] showing the simple mechanical relationship between pressures, segmental flow, and distention of the vascular bed in the isolated lung have started to unveil some fundamental facts about the pulmonary vascular bed but there is still much to be learned about the behavior of the pulmonary vessels in heart disease. The pulmonary circulation occupies a unique position. The constant contact with ambient air necessitates a low-pressure system. The interposition between two forceful pumps beating together but under much different demands requires a special regulation of the pulmonary vessels that has to be integrated with the performance of the pumps; the details of this integration are largely unknown. That the regulatory mechanisms are of great importance is demonstrated by the prompt adjustment of output which one ventricle makes when the other is failing, an arrangement necessary for the continuation of life. The importance of the pulmonary vascular bed lies also in the fact that it usually informs the patient that something is wrong with his heart and may quickly throw him into an attack of pulmonary edema.

It is easy to imagine that the symptoms occurring in left ventricular failure and originating in the lungs are due to the distention of the pulmonary vascular bed by an increased volume of blood. That this is so has not been demonstrated, however. Soon after the introduction of more exact methods for the study of the pulmonary circulation in man, we demonstrated that pulmonary symptoms in heart disease were due more to the increased pressures in the pulmonary vascular bed than to the alteration of the central blood volume, an admittedly uncertain distinction.[13] With more exact methods for the determination of pulmonary blood volume, it has been shown to vary within wide limits in patients with left heart disease, with no clear relation to the severity of the heart damage and without any correlation to the blood pressures in the pulmonary circuit (Fig. 1).[8]

An attempt was made to reproduce some

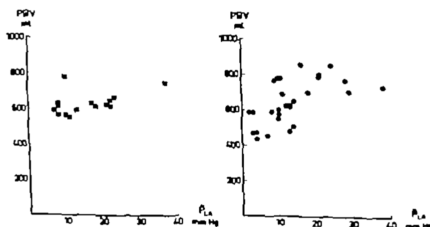


Fig. 1. The relationship between pulmonary blood volume (*PBV*) and blood pressure in the left atrium in two series of patients with left heart disease of varying severity. (From Forsberg, Acta Medica Scandinavica 175: Suppl. 410, 1964.)

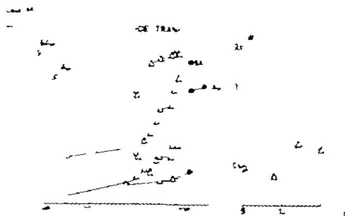


Fig. 2. Cardiac output (CO) and blood pressures in the pulmonary and systemic circuits in a patient with moderate mitral stenosis at rest and during rapid infusion of dextran corresponding to an augmentation of the total blood volume by 20 per cent. The relationship between right ventricular work (RVW) and right ventricular end-diastolic pressure (RV) is plotted to the right.

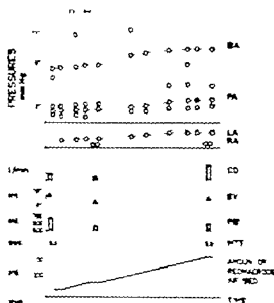


Fig. 3. Cardiac output (CO), pulmonary blood volume and blood pressures in a patient with moderate mitral stenosis at rest and during the rapid infusion of low molecular weight dextran corresponding to an augmentation of the total blood volume by 10 per cent.

of the features of congestive failure in patients with heart disease by rapidly augmenting the total blood volume by means of the plasma expander dextran in a series of patients with mitral stenosis not in failure. The blood pressure in the pulmonary circuit increased with a small but definite increase in cardiac output, changes at that time thought to be due to increased pulmonary blood volume (Fig. 2).[36] When a method for the determination of pulmonary blood volume became available, Varnauskas[37] repeated these studies using low molecular weight dextran, blood, or albumin solution and found similar increases in the pulmonary vascular pressure. However, he could not demonstrate any increase in pulmonary blood volume and reached the conclusion that any attempt to increase this volume leads to vasoconstriction and to a redistribution of the total blood volume (Fig. 3). Similarly, venesection of 300 to 400 ml. of blood lowered the blood pressure in the pulmonary circuit without changing the pulmonary blood volume (Fig. 4). This demonstrates that the autonomic nervous system may also influence the pulmonary vascular bed and emphasizes the close relationship between the function of the chambers of the heart, or the myocardium, and the pulmonary vasculature.

Integration of studies

During the last decades much important information has been assembled in regard to the architecture and function of the myocardium, both in the normal and failing circulation. The regulation of myocardial contraction and the influence of hormones and drugs on the performance

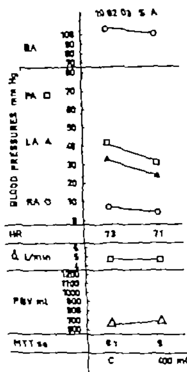


Fig. 4. The same observations as in Fig. 3 in a patient with mitral stenosis in pulmonary edema before and after the removal of about 300 ml. of blood (less than 10 per cent of the total blood volume). The clinical state improved.

of the heart have been intensively studied providing much new knowledge.

The function of the kidneys in the normal individual in animals with experimental failure and in patients with heart disease with or without failure has been described in great detail, and new hormones and regulatory mechanisms linking the adrenals and the kidneys have been discovered. The interplay between kidney and adrenals and the role of this in the maintenance of homeostasis has been successively unveiled in a fascinating series of studies.

These are examples of important details in the total picture of congestive failure. More such details have to be studied but the time may now have come when emphasis should be put on the regulation and integration of the circulatory system. The heart should supply the organism with a flow of blood adequate to give to the tissues substances necessary for their function and simultaneously to remove products created by metabolism. In order to fulfill this function and adjust the necessary expenditure of energy to what is really needed by the tissues at every moment several mechanisms must be operating both *locally* in the myocardium and in the periphery and *generally* as cardiovascular reflexes or hormonal influences. Many of these mechanisms are known or can be speculated about, but there are still many that are unknown. In most, perhaps all cases of heart disease enough mechanical work can be produced by the myocardium to provide for the basal metabolic needs of the organism. It is only when orthostatic influences, physical work, psychic strain or inflammatory reactions increase the demand on the circulation that signs of failure eventually appear. This is a fundamental fact that has important consequences for both the discussion of the pathophysiology of congestive failure and the treatment of patients with heart disease. Several features of the pathophysiology and the development of congestive heart failure have a suggestive similarity to what is seen during exercise in the normal individual. The mechanisms which adjust the circulation in normal man to the needs arising during exercise may thus be the same as those which adjust the peripheral circulation, already at rest, to the decreased ability of the central pump when heart disease is present. Failure of the circulation in the course of heart disease can never be only a failure of the heart as a pump but must imply also a failure of these mechanisms to adjust properly to the weakened myocardium. It is then the continuous attempts to adjustments which lead to the clinical picture of congestive failure.

In view of this it is regrettable that only a few studies have been made of the circulation in patients with congestive failure under a specified amount of stress. Blood volume, cardiac output, cardiac volume and intracardiac or vascular pressures are all measurements that depend not only on the presence or absence of failure of the myocardium but also on the degree of activity or stress requiring increased blood flow at the time of study. Although many methods are only valid in a steady state failure is a fleeting state that may be developing or regressing at the time at

which a study is being made. Lack of definition and clear description of the stage in the development of congestive failure invalidates many studies.

In conformity with this lack of thinking about the dynamic features of heart failure, too little attention has been paid in the past to the fact that the clinical picture of the failing heart develops over a certain period of time that usually can be counted in weeks or months rather than hours. During this time the demand on the circulation and on the central pump varies considerably and may sometimes be quite great. When the demand is increased—during physical activity or psychic stress—the ordinary regulation of the circulation which aims at the most optimal distribution of blood flow between different organs comes into play. The only exception to this slow development occurs when there is a sudden major catastrophe in the central pump, such as a large myocardial infarction or the rupture of a valve leaflet lending to congestive failure in a matter of minutes. Even in such cases this picture usually develops only if the circulation has been inadequate in situations of stress before this catastrophe strikes the pumping mechanism. This dynamic aspect of the evolution of the failing state would explain why failure does not develop in the completely resting subject. It implies that the interaction between the central pump and the periphery, activated during stress, creates a vicious circle that leads to the retention of salt and water, edema, and congestion.

What really constitutes congestive failure may seem to be fairly clear. When all different features of this clinical syndrome are taken into consideration, the difficulties become more apparent. As repeatedly demonstrated by Eichna and his group, mere congestion in the presence of heart disease cannot be taken as a sign of failure,[8] and regression of the congested state is not necessarily a sign of improved cardiac function. When Davis and associates[34] by giving minute amounts of angiotensin intravenously to dogs with large arteriovenous fistulas immediately initiated a marked positive sodium balance with edema and increase in body weight, this could not be called congestive failure, just as increased filling pressures in the heart when the blood volume is rapidly augmented[34,35] do not constitute signs of failure of the ventricles. In these instances the absence of failure is shown by the rapid reversion to normal as soon as the experimental procedure is interrupted.

On the other hand, the state of the dogs with arteriovenous fistulas during infusion of angiotensin seems to be exactly the same as that when they subsequently develop the clinical picture of failure spontaneously. Our lack of knowledge in regard to the signals between myocardial performance and the pulmonary circulation on the one hand, and the peripheral circulation and the system of kidney-adrenals and sodium metabolism on the other, is obvious. The establishment of some hormonal or neural connection between these systems of circulatory regulation is necessary before we can comprehend the details in the chain of events leading to the clinical picture of chronic congestive failure.

It seems to be probable that different cardiac lesions ought to lead to the same ultimate picture of congestive failure through varying physiologic mechanisms. The patient with mitral stenosis who has marked left atrial dilatation and severe derangement of the pulmonary circulation during the course when the right ventricle is put successively under strain certainly presents a problem different from that of the patient with aortic incompetence in whom the left ventricle has early to work under conditions implying a strain of volume overload. The patient with very rapid and sudden tachycardias that may lead to failure, even though the myocardium and valvular apparatus seem to be normal, constitutes a third, widely different type of case. Different trains of events relative to the development of changes in both the pulmonary and peripheral circulations, total blood volume, as well as in myocardial metabolism must be expected in those instances.

Future developments

Investigation of patients with the fully developed syndrome of congestive failure has provided much important information. It is not likely, however, that more intensified studies of this end stage of cardiovascular disease, even if more refined meth

ods are placed at our disposal will give more fundamental knowledge in regard to the nature and mechanisms of the disorder Instead the most fruitful approach to the problem must be directed as follows

1 Investigation must be made of the basic mechanisms governing the circulatory performance of the heart, pulmonary circulation and peripheral circulation, in all of its implications. We already have examples of this type of research, disclosing the interplay between kidneys, adrenals, and the systemic circulation

2 Future research into the mechanisms behind the development of congestive heart failure not only has to take into account the feed back loops described by Lysle Peterson that govern the properties of the vascular wall but also must consider in what way and to what extent similar feed back systems are operating in heart muscle properties, heart function, heart rate, and blood volume, both total and pulmonary The complexity of the emerging picture is great but not so great that it does not constitute an adequate and stimulating challenge to physiopathologists, biophysicists, and biomathematicians, now and in the future.

3 Another equally important avenue of investigation is the comprehensive study of patients with heart disease *before* they develop the syndrome, studies that should be repeated regularly in order to define the physiologic background of the sequence of events leading to the congested state. This should be done in man in patients, which necessarily will make it a difficult and arduous task.

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Fundamentals of clinical cardiology

Methods for studying the influence of higher central nervous centers on the peripheral circulation of intact man

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Psychologic factors influence the cardiovascular system. Hypertension, angina pectoris, pulmonary edema, acute myocardial infarction, and even death may be precipitated by emotional disturbances.[1-4] In general, physicians are apt to consider only strong emotional stimuli such as fear, anger, and intense anxiety to play an important role in producing cardiovascular reactions. However, there is evidence that extremely subtle and mild psychologic stimuli may also produce alterations in cardiovascular function.[5] Indeed, Gantt and his group have shown that orienting and conditional reflexes may influence a variety of cardiovascular functions.[6-8] Because of a lack of interest in such problems very little effort has been made to apply Pavlovian methodology to the study of the influence of orienting and conditional stimuli on the cardiovascular system of normal and diseased man. The study of orienting and conditional reflexes in man is difficult because the moment that man is placed in an experimental situation reflexes are initiated which can modify the reflex being studied. In terms of the cardiovascular system, few measurements can be made which do not disturb the subject. Thus, studies of the effect of orienting and conditional reflexes on the cardiovascular system have been limited largely to measurements of heart rate and skin resistance or to T wave changes in the electrocardiogram. Such measurements provide only limited information. The purpose of this paper is to describe briefly two techniques for obtaining quantitative data on the peripheral circulation which are sensitive and simple, and which are especially well suited for use with Pavlovian methodology *applied to intact man*. These techniques are digital rheoplethysmography and the measurement of pressure within an isolated venous segment of the forearm of man.

The digital rheoplethysmogram

The digital rheoplethysmograph is ideally suited for the study of the influence of higher nervous centers on the peripheral circulation of intact man and other animals for the following reasons: (1) The rheoplethysmographic record can be obtained without disturbing the subject. (2) The method is quantitative, simple, accurate, reproducible, and extremely sensitive. (3) The sensitivity of the recorder can be varied to measure either gross changes or

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extremely small changes (volume change of <0.01 cubic millimeter) in the peripheral circulation. (4) The technique itself does not disturb the subject. (5) Responses to stimuli are recorded instantaneously, i.e., there is no appreciable lag between the time of application of the stimulus and the response. (6) Rheoplethysmography may be applied to man with absolute impunity.

The theory and principles of digital rheoplethysmography have been presented in detail elsewhere[7] and will be described only briefly here.

Method. Portions of any digit, for example, the second and third right finger tips (2RF and 3RF, respectively) distal to the major dorsal and palmar creases at the terminal interphalangeal articulation, are enclosed within plastic cups by means of a special resilient and nonrestricting sealing compound (Fig. 1). A pneumatic occluding cuff approximately 6 mm. in diameter is wrapped loosely around one digit, generally 2RF, just proximal to the plastic cup (Fig. 1). The cups are connected by means of rubber tubing to suitable sensitive galvanometers of the rheoplethysmograph which record simultaneously and for a single pulse cycle the volumes of digital inflow (I_V), outflow (O_V), and difference between inflow and outflow (D_V). By means of suitable

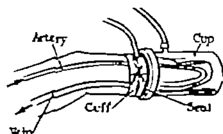


Fig. 1. Schematic representation of the digital preparation for rheoplethysmographic recording. The portion of the digit distal to the major dorsal and palmar creases at the terminal interphalangeal articulation is sealed within a light-weight plastic cup. The cup is connected by means of rubber tubing to a suitable recorder. A pneumatic occluding cuff is wrapped around the digit, just proximal to the cup, in a snug but not binding fashion. The cuff is connected to an air-pressure control solenoid by means of which it is possible to interrupt digital outflow at any predetermined moment in the pulse cycle.

RHEOPLETHYSMOGRAPHIC CONCEPT

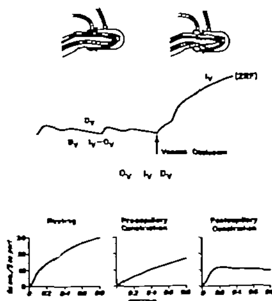


Fig. 2. Diagrams illustrating the response to inflation of the occluding cuff to a pressure of 60 mm. of Hg, which occludes the digital veins and obstructs the outflow of blood from the digit without interfering with digital inflow of blood. Therefore, upon venous occlusion, blood accumulates within the digit, and the volume of inflow is recorded. The contour of the time course curve of inflow (I_V) varies with the state of the digital blood vessels, as indicated in the lower portion of the illustration. Consult the text for details.

differentiating and difference electronic amplifiers the rates of digital inflow (I_R) and outflow (O_R) and the difference between I_R and O_R (D_R) are also recorded simultaneously with the volume traces.

The volume and rate of inflow are obtained by inflating the occluding cuff to a pressure of 60 mm. Hg (Fig. 2). With inflation of the occluding cuff, digital venous return is obstructed but digital arterial inflow is not disturbed. Thus, blood accumulates in the collecting or capacitance vessels (mainly veins) of the finger tip. For reasons described elsewhere,[7] quantitative measurements are usually made for the first complete pulse cycle after venous occlusion.

The state of the peripheral circulation varies constantly from moment to moment. Because of the great sensitivity of the rheoplethysmographic method, even the slightest variations in the peripheral circu

lation can be measured. As with any sensitive technique, it is essential that the normal variations be well understood and that environmental influences other than those being measured be completely eliminated. Thus, the examining room should be quiet and maintained at a constant, comfortable temperature and humidity and should be made to appear as unlike a laboratory as possible.[*]

Application. Because of the extreme sensitivity of the various segments of the digital blood vessels to psychogenic stimuli, digital vascular responses to many types of

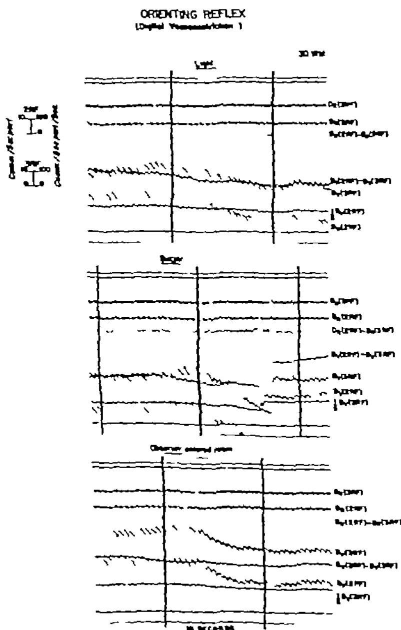


Fig. 3. The influence of various orienting stimuli on digital vascular volume. Flashing a light, sounding a buzzer or having an observer enter the room was associated with an almost immediate vasoconstriction reflected by the decrease in digital volume indicated by the sudden decline in the base line of the rheoplethysmogram for 2RF and 3RF (Dr).

stimuli can be studied and quantitated by means of the rheoplethysmographic method. In the discussion to follow, selected responses to various stimuli are presented merely to illustrate the nature of these responses and to show the ease with which the rheoplethysmographic method can be applied to the study of conditional reflexes. Furthermore, with experience, it becomes easy to detect anxiousness or psychic tension in a patient by merely observing directly the behavior of the recording galvanometer as it inscribes the pulse wave and alpha and beta deflections and as the measurements of flow are obtained. These waves and deflections have been described quantitatively.[19]

Flashing a light, sounding a buzzer, or

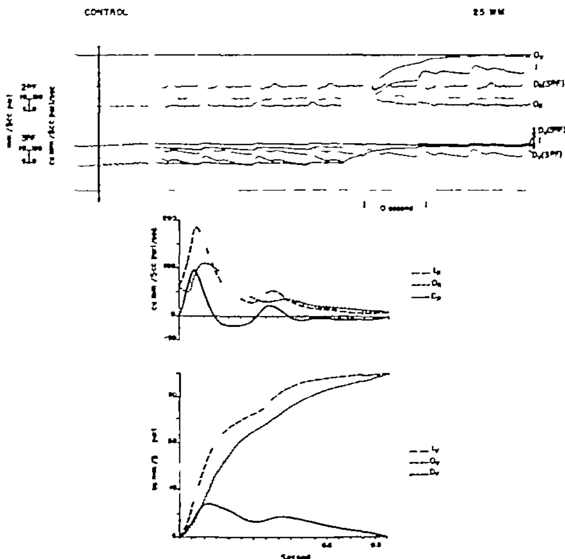


Fig. 41. Digital RPG for 2RF and 3RF obtained from a normal 25-year-old subject. The simultaneous time course curves of volume and rate of digital inflow, outflow, and difference between inflow and outflow for 2RF are shown below the original record. *I* represents volume inflow; *O*, volume outflow; D_T, difference between volume of inflow and volume of outflow; I_R, rate of inflow; O_R, rate of outflow; and D_R, difference between the rates of inflow and outflow. The paper speed was increased just before the collecting cuff was inflated. (From Burch: Psychosomatic Medicine 23:403, 1961.)

having an observer walk into the subject's room results in a marked reduction in digital volume and pulse volume as well as in a change in magnitude and configuration of the alpha and beta deflections (Fig 3) The vascular reactions promptly follow the various stimuli, so that influencing factors other than the delivered stimuli cannot be responsible for these digital vascular responses. The reduction in digital volume is probably due to both precapillary and postcapillary constriction [1] Measurements of digital blood flow during the vascular response to a stimulus such as the flashing of a light, indicate that in addition to a reduction in digital volume there is a decrease in the volume and rate of digital blood flow (Figs. 4A and 4B) The contour of the time course curve of blood flow into the digit (I_T) after delivery of an unconditional or orienting stimulus indicates precapillary vasoconstriction, reflected by the low rate of inflow and low basal pulsatile flow However the marked reduction in total digital volume indicates that the postcapillary vessels also constrict. The methods used to quantitate the magnitude of the responses have been described

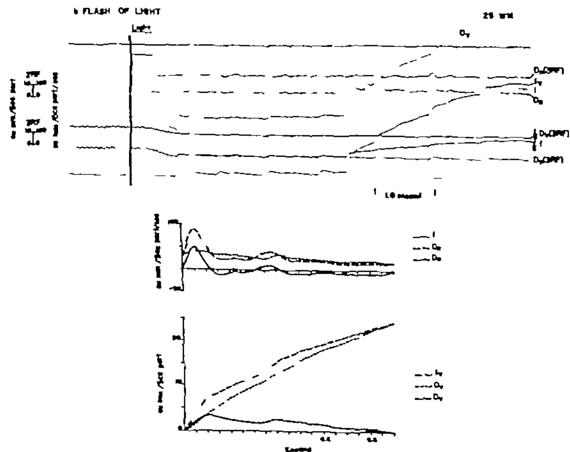


Fig 4B Digital RPG for the same subject as shown in Fig 4A The pneumatic occluding cuff was inflated a few seconds after flashing a light in the examining room. Prior to venous occlusion, the flashing of the light was associated with a marked decline in the base line of the volume traces for 2RF and 3RF The I_T curve recorded when the base line for RF reached its lowest point is of the type which reflects precapillary vasoconstriction (see Fig. 2) in that although the rate at which blood accumulates in the finger tip is slow (compare with Fig 4A), blood accumulates in the digit during the entire pulse cycle. (From Burch, Psychosomatic Medicine 23 403 1961)

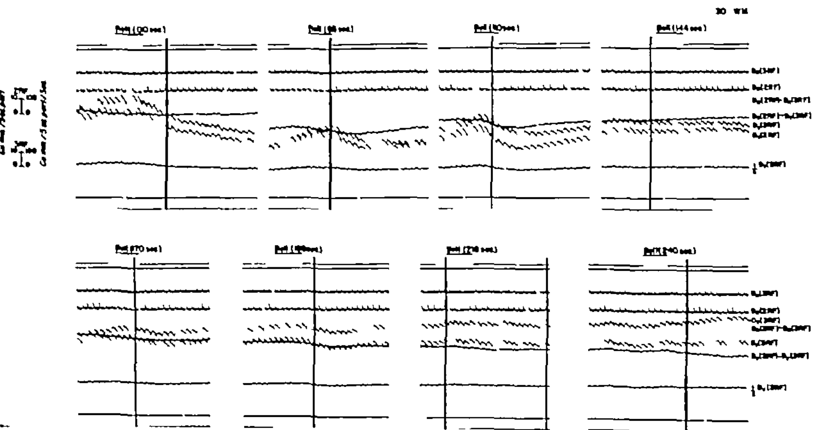


Fig. 5. Digital vascular responses to repetition of the same stimulus (ringing a bell). At first, the ringing of a bell was associated with a decline in the base line of *Dr* (2*RF*) and *Dr* (3*RF*) due to constriction of digital blood vessels. However, with repetition of the stimulus the vasoconstrictive response diminished in magnitude and finally disappeared (habituation or adaptation). (From Burch: Psychosomatic Medicine 23:403, 1961.)

elsewhere[1,18] and cannot be described in this brief report.

Casual flashing of a light or sound of a buzzer or bell are classic unconditional stimuli. Although we have not attempted to study conditional reflexes in man by means of the rheoplethysmograph, the suitability of the rheoplethysmograph for studying the influence of such reflexes on the peripheral circulation is evident.

The rheoplethysmographic technique may also be used to study other reflexes which involve higher nervous centers. One of the most interesting of these is the orienting reflex, which is initiated by any change in the subject's environment that arouses a questioning reaction. Extremely mild stimuli may result in profound peripheral vascular responses. For example, a faint tapping on the wall of the observation room or the ringing of a telephone in the distance may produce a reduction in the volume and rate of digital inflow secondary to constriction of digital blood vessels.[19] Both the intensity of the stimulus necessary to evoke the digital vascular component of an orienting reflex and the magnitude of the vascular response vary a great deal from person to person and from time to time in the same preson. Surely such responses of varying intensity occur many times during an ordinary day of a man's life. The effect of such responses on patients with serious cardiac disease needs to be investigated. Furthermore, elucidation of the reasons for the individual variations in the magnitude of the vascular response to an orienting stimulus may provide important information concerning the influence of higher nervous centers on the circulation. In this regard, repetition of an orienting stimulus usually results in gradual extinction of the orienting response (habituation or adaptation phenomenon) (Fig. 5). The ease with which habituation or adaptation is produced varies widely from individual to individual. Again knowledge of the basis for such individual variations may provide important clues concerning the role of the higher nervous centers in cardiovascular reactions.

Comment. The influence of orienting and conditional reflexes on the peripheral circulation is virtually unknown. A digital vascular response to orienting stimuli can be readily demonstrated. It is not unreasonable to suggest that vasomotor changes similar to those that occur in the digits occur also in other vascular beds in response to orienting stimuli. Because the rheoplethysmographic technique is extremely sensitive and can be applied without disturbing even conscious intact man, it is ideally suited for use with Pavlovian methodology. Only a few selected samples of the the type of digital vascular responses which are elicited by well known unconditional stimuli are shown. No attempt has been made in this laboratory to study the effect of conditional reflexes on the circulation. This presentation represents an effort to indicate to those trained in and concerned with Pavlovian methodology that a simple, sensitive, and quantitative technique is available which can be adapted to the study of the influence of conditional and other reflexes of the higher nervous system on the peripheral circulation.

Isolated venous segment

It is possible to isolate from the circulation a segment of a superficial vein of the forearm of intact man.[15,16] Under such conditions blood flow and continuity with the remainder of the circulation are eliminated, so that the changes in pressure reflect directly the changes in tone of the smooth muscle of the isolated venous segment.

Method. A venous segment about 2.5 cm. or less in length is located on the volar surface of the forearm. When a possible segment is located, the proximal and distal boundaries of the segment are marked on the skin with ink, and the segment of vein is carefully examined to be certain that it is free of valves and tributaries. The absence of tributaries can be determined by first occluding the vein with the finger tips at the boundaries of the segment (skin markings) (Fig. 6) and then pressing on the isolated segment. If no tributaries exist, the segment will remain firm and full upon compression, as shown in Fig. 6. If venous valves are present, they can usually be seen.

Once an isolated venous segment free of valves and tributaries has been selected, the segment is cannulated with a 24-gauge needle connected by means of polyethylene tubing to a strain-gauge transducer and

SELECTION OF AN ISOLATED VENOUS SEGMENT

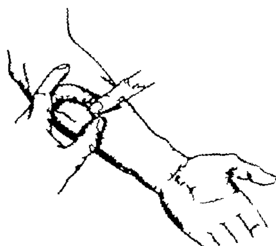


Fig. 6. Method of locating a venous segment free of tributaries and valves. The boundaries of the segment are occluded with the finger tips. If no tributaries are present, the segment will remain firm and full of blood upon digital compression. As a check, the segment is completely emptied by occluding its distal end and milking the blood out of the segment with the finger and quickly occluding the proximal end. If no tributaries are present, the segment will remain empty.

suitable recorder in order to monitor constantly the pressure within the segment (Fig. 7). Brass wedges are then placed on the segment at the levels of the skin marks. The proximal isolating wedge is put in place before the distal wedge (Fig. 8).

After the wedges are in place, segmental venous pressure is recorded continuously without disturbing the subject. Clotting of blood in the needle can be delayed by drawing heparin into the needle before cannulating the vein. Pressures have been recorded continuously under such circumstances for several hours without clotting occurring in the needle.

As segmental venous pressure is being monitored, the observer may leave the room in order not to disturb the subject.

The brass wedges produce no discomfort to the subject. However, because the subject is somewhat disturbed when stuck with the small hypodermic needle, it is necessary to wait until the pressure within the segment becomes stable before any studies are made.

Application. Flashing a light, sounding a buzzer, or ringing a bell results in an increase in segmental venous pressure (Fig. 9). The magnitude of the response to these stimuli varies a great deal from person to person. The duration of the response varies considerably.

Orienting stimuli provoke neuropsychogenic reflexes which result in increased venous tone (Fig. 10). The veno-tightening response to an orienting stimulus can be eliminated by repetition of the orienting stimulus (habituation or adaptation) (Fig. 9). Spontaneous variations in venous tone occur constantly even in a subject who is at complete rest in a comfortable, quiet room of constant temperature and humidity. It is probable that at least some part of the spontaneous variations in venous tone are due to mental processes independent of lower level neurogenic reflexes. In this regard, a simple mathematical calculation on the part of the subject may result in a marked increase in venous tone (Fig. 11). In addition, marked increases in venous

MEASUREMENT OF VENOUS PRESSURE IN ISOLATED VENOUS SEGMENT

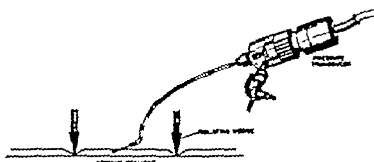


Fig. 7. Representation of the method of recording pressure in an isolated venous segment.

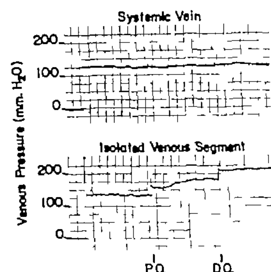


Fig 8 Changes in segmental venous pressure upon application of brass wedges. Placement of proximal (*P.O.*) and distal (*D.O.*) wedges. (From Burch: Physiological Reviews 40:50 1960.)

tone may be elicited by certain emotionally charged words (Fig 12) The relationship of conditional and orienting reflexes to spontaneous variations in venous tone needs to be studied.

On several occasions we have been successful in conditioning the venous segment. Fig 13 shows the response of the isolated venous segment to a conditional (number) and unconditional (electric shock) stimulus. The conditional response became extinct quickly but could be reinforced readily (Fig 13)

Comments Changes in venous tone in response to environmental stimuli are of importance in clinical medicine. Approximately 80 per cent of the circulating blood volume is contained within the venous system A relatively slight increase in venous tone associated with a decrease in the capacity of the venous reservoir may result in relatively large shifts of blood In the presence of a poorly functioning left ventricle a large increase in systemic venous return secondary to peripheral venous constriction may result in acute left ventricular failure and pulmonary edema It would be of importance to know to what extent psychogenic reflexes influence venous tone from moment to moment in man Such reflexes may be responsible for some instances of sudden death or acute pulmonary edema in patients with severe cardiac disease.

Discussion

Psychogenic stimuli are known to affect the circulation. Physicians are accustomed to consider such stimuli in terms of overt behavior patterns, such as rage, fear anxiety etc. However it is probable that many stimuli which influence the circulation go unnoticed These stimuli may be so subtle or mild that they produce orienting reflexes completely devoid of a motor component but associated with profound vascular changes. Other stimuli may produce vascular reactions without the subject being conscious of the stimuli because the individual has become conditioned to these stimuli.

An example which is perhaps too obvious, of the deleterious effect of psychogenic

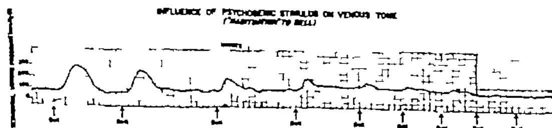


Fig 9 Effect of ringing bell on pressure in the segment, a reflection of venous tone Upon repetition of the stimulus, the magnitude of the response gradually diminished until ringing the bell no longer elicited change in venous tone (habituation or adaptation) (From Burch and DePasquale American Journal of Medical Science 213:209 1962.)

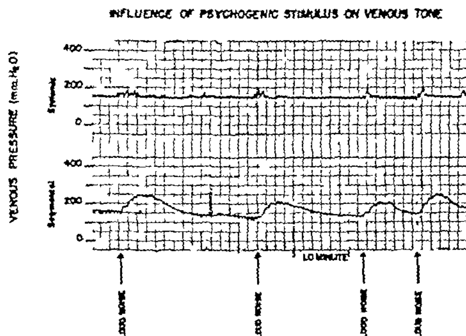


Fig. 10. Influence of a psychogenic stimulus (loud noise) on segmental and systemic venous pressures. The disturbances in the trace of systemic venous pressure are due to movement and represent a motor rather than a vasomotor response to the stimulus. Venomotor response to the stimulus is indicated by the segmental venous pressure trace. (From Burch and DePasquale: American Journal of Medical Science 243:209, 1962.)

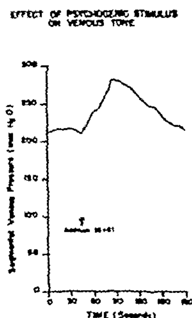


Fig. 11. Influence of mathematical calculation on segmental venous pressure.

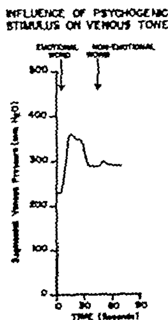


Fig. 12. Influence of an "emotionally charged" word on segmental venous pressure. (From Burch and DePasquale: American Journal of Medical Science 243:209, 1962.)

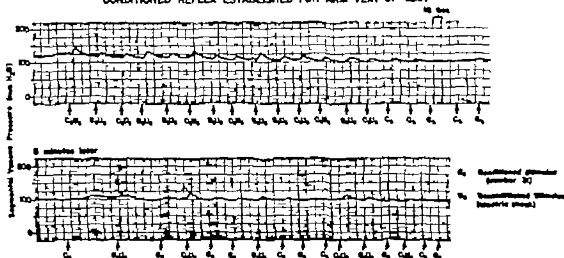


Fig. 13. Influence of a conditional stimulus (C_s) followed by an unconditional stimulus (U_s) on venous tone. After continued repetition of the two stimuli, presentations of the conditional stimulus alone resulted in an increase in segmental venous tone.

stimuli on the circulation is recounted here. An elderly white male patient was seen by us on Christmas Eve of 1960. He had had an extensive myocardial infarct and was in cardiovascular collapse. The blood pressure could be maintained with norepinephrine. He was doing fairly well until a priest who had been summoned by his family walked into the room. Upon seeing the priest the patient suddenly became cyanotic and died. The mechanism of death can only be speculated upon, but clinically it was thought to be due in part to sudden hemodynamic alterations associated with a sudden increase in systemic venous return. Although learned associations, such as those of priest, last rites, and death are fairly obvious, other more subtle stimuli must influence the circulation many times throughout the day. The study of cardiovascular reactions to psychogenic stimuli, and studies on the extent to which cardiovascular reactions can be conditioned are of practical as well as theoretical importance. Ideal management of the cardiac patient may not be possible until more is known concerning conditional and other higher level central nervous system stimuli which alter cardiovascular function.

Digital rheoplethysmography and the measurement of pressure within the isolated venous segment are simple and yet extremely sensitive methods for studying the response of the peripheral circulation to orienting, conditional and other stimuli. These methods have many advantages over the more conventional methods used to study vascular responses to psychogenic stimulation, such as the measurement of pulse rate, skin temperature, and skin resistance.

Summary

Although they are of clinical importance relatively few studies have been conducted on the influence of orienting and conditional reflexes on the cardiovascular system. In addition, there are virtually no studies on the influence of such reflexes on the peripheral circulation of man. One of the difficulties involved in the study of vascular responses to orienting and conditional reflexes has been the lack of techniques which are quantitative and sensitive and which can be applied without disturbing the intact man. This report described two techniques used in our laboratory to study the peripheral circulation which are ideally suited for use with Pavlovian methodology.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Antiarrhythmic drugs
Part V. Pharmacology of procaine amide

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The demonstration of the antiarrhythmic action of procaine hydrochloride solution applied topically to the exposed heart during surgery was made almost 30 years ago. Procaine solution also had limited use intravenously as an antiarrhythmic agent in anesthetized patients, but its central nervous system toxicity restricted its use to the anesthetized patient. Studies on the metabolic disposition after intravenous administration showed that procaine hydrochloride was rapidly and almost completely hydrolyzed to para-aminobenzoic acid and diethylaminoethanol by a plasma esterase. Diethylaminoethanol was found to exert an antiarrhythmic action on the heart, but its activity is considerably less than that of procaine. A number of derivatives of diethylaminoethanol were synthesized and studied for their antiarrhythmic effect. The most potent and least toxic agent in these studies was procaine amide (p-amino-N (2-diethyl aminoethyl) benzamide), a substance in which the ester linkage of procaine is replaced by an amide linkage. This drug is considerably more stable in the body than procaine and exerts antiarrhythmic action in doses having little effect on the central nervous system. It is marketed and sold under the proprietary name of Pronestyl.

The absorption of procaine amide from the gastrointestinal tract is rapid and virtually complete, and the peak plasma level of the drug is achieved usually within 2 hours after oral administration. After intramuscular administration maximal plasma levels are obtained within 1 hour. After its absorption, the plasma levels of the drug decline at a rate of only 10 to 15 per cent per hour. About 60 per cent of the drug is excreted unchanged in the urine, and about 5 per cent as free or conjugated para-aminobenzoic acid. At plasma levels of 10 to 20 mg. per liter (levels within the range of therapeutic concentration) only about 15 per cent of the drug is bound to plasma proteins, but considerable amounts are reversibly bound to various organ tissues, especially liver, spleen, lung, and heart. This explains, in part, the relatively slow decline in plasma levels, since tissue *depots* of drug serve as a reservoir as the compound is lost by excretion or metabolic transformation.

The drug does not accumulate on repeated oral dosage. Thus, on a dosage schedule of 750 mg. every 6 hours, the peak plasma level is achieved within 24 hours. To increase the plasma concentration, it is necessary either to increase the amount of the *individual* dose or to raise the frequency of administration. Patients with renal damage or with congestive heart failure excrete procaine amide more slowly than do normal persons, and cumulative effects

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are consequently more likely in such individuals.

A large number of compounds with a tertiary nitrogen in their structure can be shown to have antiarrhythmic properties in in vitro studies. These agents include local anesthetics, anticonvulsants, and antihistamines as well as procaine amide and quinidine. Procaine amide has been widely used as an antiarrhythmic agent, but the pharmacologic effects of antiarrhythmic compounds on the function of normal and abnormal cardiac tissue have been more intensively studied with quinidine than with procaine amide. Almost all studies have indicated that the cardiac effects of these two drugs are qualitatively the same, although quantitative differences exist in the effects on impulse formation, conduction time, refractory period, myocardial contractility, and peripheral vasodilation. These differences do not explain, however, the successful use of one drug when the other has failed as an antiarrhythmic agent. The systemic or noncardiac toxicity of procaine amide differs from that of quinidine, and these differences have made it a useful additional agent to quinidine in the clinical management of arrhythmias.

Procaine amide slows conduction in the atria and the atrioventricular junctional tissue and within the ventricle. This is noted in the electrocardiogram as prolongation of the P-R interval and the QRS duration. In one study, the depressant effect upon conduction was greatest across the A-V node, suggesting the greater sensitivity of this tissue to the drug. The refractory period is also prolonged by procaine amide, an important factor in terminating circus movement. The excitability of both the ventricle and atrium to electrical stimulation is depressed by procaine amide. In addition, the rate of pacemaker discharge is also depressed. There is general agreement that the mode of antiarrhythmic action of both procaine amide and quinidine is probably related to their effect upon the cardiac cell membrane and the flow of ions across the membrane during depolarization and repolarization. The studies with quinidine have shown that during depolarization there is a decreased rate of entry of sodium into the cell, resulting in both a slowing and a decrease in the depolarization spike recorded in transmembrane studies. There is also probably decreased entry of calcium into the cell. There is also decreased loss of potassium during depolarization, and during repolarization there is an increased efflux of potassium. This latter effect has been assumed to be most important in depressing the spontaneous diastolic depolarization that is characteristic of pacemaker tissue. The observations with procaine amide have been fewer in number, but those that have been made have shown that procaine amide has the same effects on ion transfer as does quinidine. Observations of a quantitative comparison between procaine amide and quinidine on the effect on ion flux in the same preparation are limited.

The effect of procaine amide upon contractility of cardiac musculature was originally thought to be less than that of quinidine. In the turtle heart, antiarrhythmic doses of procaine amide had less contractile depression and less blockade of the epinephrine effect than did equivalent antiarrhythmic doses of quinidine. More recent studies using the Walton-Brodie myocardial strain-gauge arch have compared the depressant effects of procaine amide and quinidine upon myocardial contractility of the dog left ventricle in vivo. Both agents depressed contractility equally, expressed as milligrams per kilogram, and the fact that the therapeutic doses of procaine amide are generally much larger than those of quinidine suggests that, if these experiments can be transferred to man, the effect upon cardiac contractility should be more evident with procaine amide. An additional study using the strain-gauge arch was carried out in man during cardiac surgery and compared lidocaine and procaine amide. Again, a decrease in the contractile force of the right ventricle after the administration of intravenous procaine amide was noted. Hypotension during the intravenous administration of procaine
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nificantly to hypotension These results in controlled laboratory and operating room investigations require consideration in the clinical use of antiarrhythmic agents. In many cases, the temporary arrhythmia causes severe cardiac dysfunction, and the most urgent problem is to restore normal cardiac rhythm This is particularly true of ventricular tachycardia. In dogs, ventricular tachycardia has been produced by narrowing and ligation of the coronary artery Procaine amide was effective in correcting this arrhythmia, without evidence of decreased cardiac contractility Similarly patients who have been on large maintenance doses of procaine amide for many months and years have not shown particular evidence of cardiac failure Toxic effects upon myocardial contractility may be more difficult to recognize than toxicity expressed as fever rash granulocytopenia, etc.

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Aortic valve surgery and autoimmune hemolytic anemia

Hemolytic anemia has occasionally been reported as complicating various open-heart surgery procedures performed in experimental animals and human beings. In recent years the insertion of an aortic valve prosthesis has led to several reports of clinically significant hemolytic anemia. These cases have been characterized by destruction of erythrocytes through mechanical means. We have recently encountered 7 cases of acquired hemolytic anemia after aortic valve surgery which did not appear to result solely from mechanical breakdown of erythrocytes. The association of positive serologic tests and a characteristic clinical pattern appears to indicate a previously undescribed syndrome. The purpose of the present report is to outline the clinical nature of this state and to indicate a possible autoimmune pathogenesis for the hemolytic process.

Certain similarities in the clinical pattern of these cases can be noted and are summarized as follows: (A) All 7 cases involved the insertion of a Starr-Edwards artificial aortic valve. In 2 cases the mitral and tricuspid valves were also replaced. In another case replacement of the mitral valve was made in association with the aortic valve. (B) The hemolytic anemia was an early clinical complication generally occurring within 3 weeks after the surgical procedure. (C) In all cases anemia and reticulocytosis were a prominent part of the clinical picture. Erythrocyte morphology was carefully examined in 5 of the 7 cases, and an essentially normal morphologic picture was found. Fragmented erthrocytes as previously described in mechanical hemolytic anemia were not a diagnostic finding. Examinations of bone marrow revealed a hypercellular picture with marked erythrocytic hyperplasia. Elevation of serum bilirubin was variable and of little aid in the diagnosis of the hemolytic state. (D) The hemolytic anemia either occurred as a transient phenomenon or was long standing with episodes of exacerbation and remission. In the latter instance, stabilization of the hematocrit and an elevated reticulocyte count generally occurred. (E) Although the hemolytic syndrome appeared to be very severe, it did not result in the death of any of the patients or jeopardize the cardiovascular benefit resulting from the operative procedure. (F) No ancillary preoperative state or postoperative complications appeared to be universally associated with the development of the hemolytic anemia. The febrile-lymphocytosis-splenomegaly syndrome however was present in 4 of the 7 cases in which hemolytic anemia developed. (G) Corticosteroid therapy was utilized in 4 of the 7 cases. In all 4 cases a successful therapeutic response was apparent.

Positive direct antiglobulin (Coombs) tests were obtained in 6 of the 7 cases. An indirect antiglobulin (Coombs) test was also positive in 2 cases. Direct and indirect proteolytic enzyme tests (bromelin) paralleled, in a weaker fashion, the results of the antiglobulin procedure. The nature of the globulin resulting in the positive antiglobulin and bromelin test is of great theoretical interest in the pathogenesis of hemolytic anemia. This material was eluted from the erythrocyte surface in 2 cases, and immunohematological studies were carried out. The following serologic conclusions can be drawn: (A) The reactivity of the direct antiglobulin and bromelin tests was generally weak, ranging from trace to 2+ reactions. (B) Commercial antiglobulin sera was found to be highly variable in its ability to detect the positive serologic state. It is suggested that either a selected potent antiglobulin sera be used or else several different reagents be employed when the characteristic clinical state is seen. (C) The positive serologic test may be transient, persisting for only a week or so in some cases. In others, the serologic tests may persist for over 1 year, even when overt hemolysis is absent. (D) The antibody appeared to be a panhemagglutinin reacting with all erythrocytes in our test panel. Accordingly, the coating material leading to the positive serologic test functioned as an autoantibody reacting with normal erythrocytes as well as the patient's erythrocytes. (E) The autoantibody was inhibited by streptomycin to a degree similar to that seen with other erythrocyte autoantibodies characteristic of acquired hemolytic anemia. (F) Treatment of the incomplete autoantibody with 2-mercaptoethanol resulted in its conversion into a saline-acting form as previously described with autoantibodies. The degree of conversion of the incomplete form into the saline type was at a level comparable to that seen with Rh antibodies and erythrocyte autoantibodies.

Although hemolytic anemia has previously been described as complicating open-heart surgery, a purely mechanical destruction of red cells has been the usual mechanism. The cases reported here do not appear to fit this mechanical category in view of the following facts: (A) In 6 of the 7 cases the antiglobulin and/or bromelin tests were positive. (B)

Corticosteroid therapy in 4 cases was of aid in correcting the hemolytic process. (C) In several cases only a transient hemolytic syndrome was seen, with spontaneous recovery. (D) Surgical exploration and correction of the valve prosthesis was not necessary.

Certain negative conclusions in regard to the pathogenesis appear to be warranted. (A) The antiglobulin positive state is not due to a modification of the erythrocyte surface that permits normal globulin to react with and fix to the erythrocytes. The studies carried out on antibodies indicate that the positive antiglobulin reaction is due to the presence of a true autoantibody with the ability to fix to normal erythrocytes. (B) The material composing the Starr-Edwards valve[9] is not intimately involved in the development of the autoantibody through a haptene or drug-sensitivity relationship. Well over 100 such valves have been inserted into the mitral area at our institution, without the development of a similar hemolytic syndrome. (C) Ancillary technical or clinical states peculiar to our own institution are not concerned in this phenomena. Högman[10] has studied in detail one case at Uppsala. The autoantibody had the specificity of anti-hr (e) and was apparently not involved in a hemolytic syndrome. (D) The hemolytic syndrome is not directly related to rheumatic heart disease. In 3 of the 7 cases there were congenital aortic valve deformities.

The presence of erythrocyte autoantibodies suggests an autoimmune pathogenesis for the development of the hemolytic anemia. The relationship between autoimmune hemolytic anemia and aortic valve surgery, however, is obscure. Two possibilities appear to deserve further investigation. Four of the 7 cases of hemolytic anemia developed the febrile-lymphocyte-splenomegally syndrome as described by Seaman and Starr.[11] Although the etiology of this complication is still unknown, it appears to be probable that abnormal lymphocytes are involved in the pathogenesis. It is possible that the large volume of fresh blood transfused during the operation introduces many viable foreign lymphocytes.[12] If such a state truly exists, the persistence of such lymphocytes could permit the development of a graft-host (runt disease) phenomena with one of the target organs appearing as the patient's erythrocytes.[13] The ability of the foreign lymphocytes to survive in the patient's circulation would determine the length of time for the persistence of the hemolytic disease. The major discrepancy in this attractive hypothesis is the lack of evidence for a similar autoimmune hemolytic anemia developing in patients undergoing other open-heart surgical procedures in which a similar volume of transfused blood is utilized.

The observation that aortic valve surgery seems to predispose to the development of an autoimmune hemolytic anemia suggests that mechanical damage to the erythrocyte may be an important factor. The extreme turbulence of blood flow in severe aortic stenosis, as well as the turbulence present after valve prosthesis supports this possibility. Such mechanical trauma to the erythrocyte surface may lead to changes in the erythrocyte membrane which could involve various surface antigens. The modified antigen may appear to be foreign to the host and antibody formation is initiated. The antibody formed would react with the patient's own erythrocytes, appearing as an autoantibody. In all probability, such an antibody would appear as a cross-reacting substance capable of reacting with all human erythrocytes. If such a pathogenesis exists, we would anticipate encountering autoimmune hemolytic anemia as a complication of various cardiac states predisposing to extreme turbulence of blood flow. Some evidence for this situation now exists. We have now studied 2 cases with positive antiglobulin and bromelin tests discovered prior to operation.

It should be emphasized that not all hemolytic anemia which may complicate cardiac surgery will appear as an autoimmune phenomenon. Mechanical damage to erythrocytes leading to their lysis must still be considered. The high incidence of an autoimmune hemolytic anemia complicating aortic valve surgery, however, deserves further investigation. The delineation of the exact mechanism leading to erythrocyte autoantibody formation will be of great value in our eventual understanding of autoimmune states.

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Mitral valvotomy and pregnancy

As maternal mortality has fallen dramatically over the past 40 years the importance of heart disease in pregnancy has increased and it now ranks high among the causes of death during pregnancy

The most common heart lesion in pregnancy is mitral stenosis. The value of mitral valvotomy is not in doubt but its place in the management of mitral stenosis during pregnancy is not settled Opinions range from those who believe that it should be used very rarely to those who consider that pregnancy is an added indication for operation.[1]

Marquis has shown that the medical management of pregnant patients with severe mitral stenosis has an appreciable mortality (2 5 per cent). A number of these patients underwent mitral valvotomy subsequent to delivery with an operative mortality of 4 7 per cent

The opponents of mitral valvotomy during pregnancy maintain that the assessment of the degree of stenosis and the estimation of the amount of associated mitral incompetence are more difficult during pregnancy They further suggest that the risk of operation in the pregnant patient is greater than in the nonpregnant.

In an attempt to clarify these issues, 41 patients who underwent mitral valvotomy during pregnancy were studied All of these patients were operated on because of severe symptoms. Eight had pulmonary edema 2 had congestive heart failure and the rest were in clinical Grade III or IV according to the New York Heart Association classification The stage of pregnancy at which the operation was performed averaged 23 weeks and varied from 5 weeks to 38 weeks.

These patients were compared with a similar group of women who underwent mitral valvotomy when not pregnant and whose preoperative clinical, radiographic and electrocardiographic status was similar to that of the pregnant patient before conception.

The surgical findings were similar in the two groups—both in regard to the incidence of very tight mitral stenosis and to the incidence of trivial mitral reflux. No patients in either group had significant mitral incompetence or aortic valve disease

One patient in the pregnant group died 48 hours after operation This was a moribund patient in intractable failure precipitated by chest infection who failed to respond to treatment. Early valvotomy might have saved her life No patient in the control group died at operation

Fetal or neonatal death occurred in 7 patients (17 per cent), and premature birth was associated with the operation in 6 patients (15 per cent).

After operation both groups of patients were reviewed regularly for periods up to 9 years. No deaths occurred in either group during this time. No difference was noted between the two groups in terms of clinical status over this period (6 years after valvotomy 74 per cent of the pregnant group and 78 per cent of the control group were clinically Grade I or II). A similar number in each group has required repeat mitral valvotomy

These findings have been taken to indicate that the hemodynamic changes of pregnancy do not invalidate the preoperative assessment of patients, nor increase the risk of operation. The relief of the stenosis is equally satisfactory in pregnant and non pregnant patients, and the follow-up results are similar in the two groups.

Delaying mitral valvotomy in pregnant patients often means condemning the mother to long periods of bed rest in the hospital, and increases the risk of incidental chest infections. If operation is deferred the mother is then asked to come to the hospital for the operation some time after the delivery when she is extremely loathe to leave her infant. Such course would only be advisable if it could be shown that operation during pregnancy involves a greater risk than medical management prior to delivery with subsequent mitral valvotomy

Patients with mitral stenosis are often advised to undergo mitral valvotomy before embarking on a pregnancy in order to reduce the risks of the pregnancy Information is frequently sought in regard to the effect of pregnancy subsequent to mitral valvotomy on the long-term outlook The generally accepted view is that if patients with rheumatic heart disease survive a pregnancy their natural life expectancy is not affected, although this view is not unanimous[2,3]

With this question in mind 58 patients who

underwent mitral valvotomy and later become pregnant were compared with a similar group of women who did not become pregnant. The interval between the operation and pregnancy averaged 3½ years, and the majority of patients were free of symptoms prior to the pregnancy.

No patient died during the pregnancy but 1 year after the pregnancy 36 per cent of the pregnant group were downgraded by at least one clinical grade (New York Heart Association classification), as compared with 18 per cent of the controls (statistically significant difference). The same trend was seen at later reviews, but the numbers available for comparison were small and the difference did not reach significant levels.

It was thought that the study suggested that pregnancy may increase the chances of ultimate deterioration in patients who have undergone mitral valvotomy and that the decision to embark on pregnancy in such patients should not be made lightly. However it was indicated that further studies, with larger groups of patients, are needed to settle this issue.

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Prolonged observation of pulmonary arterial pressure

Dotter and Straube, 1962, reported the use of a plastic tubing which was introduced percutaneously through a 12-gauge needle into an antecubital vein for obtaining right heart pressures. They showed that this catheter could be guided into the pulmonary artery without fluoroscopy. More recently, Fife and Lee in 1965 reported on the use of a modification of this approach to catheterization of the right heart. Fabricated from Tygon tubing, their catheter contained a thin section located 3 cm. from the distal end which enabled the catheter to be easily maneuvered into the pulmonary artery without fluoroscopy.

We have found that it is possible to pass a Teflon insulated stainless steel wire, of such size that it may be inserted through a No. 18 thin-walled needle into the pulmonary artery. This wire has been used for the identification of atrial activity in cases of difficult arrhythmias, as well as for the detection of left-to-right shunts using hydrogen and for temporary pacing in heart block. Furthermore, PE 50 to 160 tubing or vinyl tubing may be passed from either the antecubital vein or an external jugular vein into the right heart without fluoroscopy. This has been done over 200 times in animals, without difficulty.

More recently we have employed this technique for placement of a catheter in the pulmonary artery for the chronic observation of pulmonary arterial pressure. In 6 patients with chronic lung disease,

a PE 50 tubing was introduced through a 18-gauge thin-walled needle into a median antecubital vein. While the pressure was being monitored the tubing was advanced without fluoroscopy into the pulmonary artery. On occasion the catheter appeared to coil in the right ventricle. However a Valsalva maneuver frequently was helpful in moving the tip of the catheter into the pulmonary artery. The catheter was then taped to the arm, and the electrocardiogram was monitored continuously.

It was then possible to observe pulmonary arterial pressure during periods of rest as well as sleep, to observe the effects of repeated administration of drugs over prolonged periods of time and to evaluate the effect of other maneuvers such as breathing exercises, inhalation therapy, and administration of oxygen. These catheters were left in place for as long as 4 days without difficulty. No evidence of infection or embolization was noted. No anticoagulants were given. During these periods of observation in addition to samples of blood from the pulmonary artery, samples of systemic arterial blood were frequently obtained, and in one instance a polyethylene tube was left in the brachial artery for a period of 3 days, having been placed by the Seldinger technique. This enabled observation of the changes in arterial blood gases during these various maneuvers.

It is suggested that this is a simple and safe technique for the chronic observation of the long-term effect of various pharmacologic agents, sleep, and alterations in ventilation on the pulmonary circulation. Recently it has been shown that chronic pharmacologic therapy may be useful in reducing hypoxic pulmonary hypertension and in addition that the response to acute treatment does not necessarily reflect the changes possible with chronic therapy.[5] The need for such information is stressed particularly when dealing with patients who have underlying disease states affecting the pulmonary circulation. Moreover, this technique has proved to be useful in performing pulmonary arterial studies in cases in which it was not possible to enter the pulmonary artery with a standard cardiac catheter.

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Iatrogenic vertebral arteriovenous fistula

Arteriovenous communications between the vertebral vessels are usually a result of trauma. The common mechanisms are stab wounds, gun-shot wounds,[1] or occasionally indirect injury to the cervical spine.[2] There is one report of a "spontaneous" vertebral arteriovenous fistula.[3] Attention is drawn to a further cause, namely, percutaneous vertebral arteriography. We can discover in the English literature only two reports of a similar occurrence.

A 37-year-old housewife was almost certainly suffering from disseminated sclerosis which had started during pregnancy when she was 23 years old. She was investigated at a hospital in London and subjected to angiography. Puncture of the right vertebral artery was unsuccessful, but that on the left presented no difficulty. The x-ray pictures were normal. Five days later she suddenly experienced a terrifying loud and rushing noise in the right occipital and temporal region, aggravated by stooping and by turning the head. I examined her some 6 months later, when she had a very loud continuous bruit over the whole of the neck, although maximal in the right side and loudest over the upper end of the internal carotid artery. The bruit was diminished by digital compression of the right subclavian artery. There was no bruit over the orbit or skull. The blood pressure was 130/80 mm. Hg. She was then subjected to right axillary arteriography under local anesthesia. An arteriovenous fistula between the vertebral artery and its venous plexus was demonstrated. Contrast medium passed rapidly into a much dilated vertebral venous plexus draining through enlarged deep

cervical and vertebral veins Some of the contrast medium immediately crossed the midline at the C level through the external vertebral venous plexuses, outlining the plexus of veins around the left ertebral artery Drainage was rapid and the left vertebral veins could be ident fied before in jection of contrast medium into the right vertebral artery had been completed The site of the fistula was thought to be at the level of the fourth cervical ertebra, where the vertebral artery narrowed abruptly and maximal venous filling occurred. The vertebral artery could not be identified at a higher level, and no contrast medium entered the posterior fossa A neurosurgeon, a vascular surgeon and a thoracic surgeon were consulted, but none was anxious to attempt surgical treatment.

Sutton noted this complication only once in 10,000 arteriograms, and the only other reported example to be discovered is that of Olson and associates There is an understandable reluctance to publicize unfortunate complications and this may account for unreported examples this patient case was shown to the North of England Neurological Association in Leeds, in 1964 and reference was made to at least four other examples This patient case has been recorded, and the three now to be found in the literature all involve the right ertebral artery This may be coincidental, lthough the right ertebral artery tends to be smaller than the left I all three there has been an intery l between the examination and the development of the bruit. It seems probable that most patients will equire surgic l treatment, but, according to Aronson a review of operations on the ertebral artery up to 1946 disclosed mortality rate of over 50 per cent Elkin and Harris thought that the procedure of choice was exposure of the fistula by the lateral approach followed by direct obliteration they treated 10 examples of t u matic vertebral arteriovenous fistula without mortality

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Letter to the Editor

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To the Editor:

In reference to my paper "Acid-Base Balance. A Review of Current Approaches and Techniques" which appeared in the May 1965 issue of the JOURNAL, I think that several comments are pertinent. I stated that in order to obtain accurate results from venous blood samples should be taken without stasis. Additional work done in this area since the acceptance of my paper indicates that brief periods of stasis of up to 45 seconds do not significantly alter the results and make sampling much simpler.

The second point worthy of comment deals with the presence or absence of compensatory changes in the partial pressure of CO_2 and metabolic alkalosis. I stated and indicated in the diagram that no significant compensatory changes occur. This is not entirely correct. A review of the 150 cases of metabolic alkalosis over the past few years reveals that there is very *little if any* compensatory change until the CO_2 content reaches 38 to 40 millimols per liter. After this point, elevations in the pCO_2 are seen in some but not all cases. In the more commonly encountered cases of metabolic alkalosis with the CO_2s below 40 compensatory changes in pCO_2 are not the rule.

A third point which may bear on the second is that activity prior to sampling has a good deal to do with venous pCO_2. There is little comment about this in the literature, and I believe that this may be a source of disagreement as to what represents a normal value for pCO_2. We sampled 10 normal individuals who were actively engaged in their daily work and found their pCO_2s to range from 46 to 57 with a mean of 52. The same individuals were placed at rest for a period of 10 minutes and restudied. The mean pCO_2 at this time was 44 with a range of 42 to 46. I believe that in order to obtain reproducible results it is important to have the individual relatively inactive for a period of 10 to 15 minutes prior to sampling, regardless of what type of blood sample, arterial or venous, is used. One wonders whether the problem of the status of the individual prior to sampling does not play a major role in venous pCO_2 values in patients or subjects undergoing various studies. Several of the recent studies which deal with metabolic alkalosis indicate that in otherwise healthy subjects the pCO_2 is elevated in the presence of metabolic alkalosis. The authors, however, do not comment on the status of the individual prior to sampling of the venous blood. More detailed studies of this phenomenon are in progress in this laboratory and will be the subject of a later report.

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Book reviews

CARDIOVASCULAR DRUG THERAPY. Eleventh Hahnemann Symposium. Edited by Albert N. Brest, M.D. and John H. Moyer, M.D. New York, 1965. Grune & Stratton, Inc. 331 pages. Price $19.75.

This book contains the papers presented at another Hahnemann symposium held in Philadelphia in January 1964. There were many contributors and many subjects were discussed. Antihypertensive drugs, vasopressor agents, diuretic drugs, anticoagulant therapy, antianginal compounds, antilipemic drugs, cardiotonic drugs, and antiarrhythmic drugs were among the drugs and agents discussed. Most of the papers were necessarily short, since about 73 presentations by 86 contributors were delivered in 4 days. Furthermore, the fine points in therapy are not given. For example, Dr. Master wrote on the clinical evaluation of antianginal drugs in 4 pages, 2 of which consist of a long list of drugs and agents administered by doctors to their patients with angina. He made no effort to indicate for the reader his impressions of this tremendous list of agents. A few papers are good, but the book cannot be strongly recommended. This is not a critical presentation of the many problems involved in cardiovascular drug therapy.

CLINICAL TESTING OF NEW DRUGS. Edited by Arthur D. Herrick and McKeen Cattell. New York, 1965. Revere Publishing Company. 362 pages. Price $11.75.

This volume is offered as a guide to clinicians and pharmacologists who are concerned with the clinical testing of new drugs. Before a compound may be approved for clinical use, it must undergo extensive investigation, including (1) animal studies of toxicity, metabolism, excretion, and other biologic effects, (2) initial limited studies in man by a few expert investigators, and then (3) larger clinical trials involving administration of the drug to more patients under conditions approaching general medical practice. This volume reflects the broad character of these studies and contains papers on each of these various aspects of new drug testing. Pertinent federal regulations governing clinical investigation in this country are also described.

Because the text is multiauthored, the style varies somewhat in each chapter. However, in general, the individual topics are treated in editorial fashion. In this way, certain specifics are denied to the reader, but he benefits from a broader perspective look at the problems of testing involved. This volume will be useful mainly to the clinical investigator. The information contained therein should help him to plan his studies better and thereby avoid certain investigative pitfalls.

PULMONARY EMBOLIC DISEASE. Edited by Arthur A. Sasahara, M.D. and Myron Stein, M.D. New York, 1965. Grune & Stratton, Inc. 312 pages. Price $14.50.

This book includes a series of papers presented at a symposium on pulmonary embolic disease held on May 22 and 23, 1964, in Boston. It contains nothing new, but symposiums rarely do. The papers include selected aspects of the work of the contributors, most of which has already been published. Those who did not attend the symposium, and especially those who have not followed the literature on the subject, will find the review of pulmonary embolic diseases interesting. Unfortunately, much time was unnecessarily devoted to such subjects as blood coagulation and thrombosis, the pharmacology of anticoagulant drugs, fatty acids and thrombus formation, and the like. These problems are repeatedly discussed at medical meetings and symposia on coronary artery disease, cerebrovascular disease, and peripheral vascular disease, so that they are of less interest to the reader. The proceedings of the symposium should interest physicians and students who wish to become acquainted in general with the present ideas concerned with pulmonary embolic disease.

METABOLISM OF LIPIDS AS RELATED TO ATHEROSCLEROSIS. A Symposium. Compiled by Fred A. Kummerow, Burnsides Research Laboratory, University of Illinois, Urbana, Ill. Springfield, Ill., 1965. Charles C Thomas. 300 pages. Price $14.50.

This monograph includes the collected papers of a symposium presented at the dedication exercises for a new research building at the University of Illinois at Urbana in June, 1963. The papers, of course, do not contain any new material. Among the problems discussed are avenues of control of serum cholesterol, therapeutic considerations in the treatment of coronary heart disease, the natural

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Editorial

High-altitude pulmonary edema

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Until 1960 when Houston[1] recorded his case in the English literature, high-altitude pulmonary edema was little known outside the Peruvian Andes. Hurtado[2] however first reported it in 1937 in a South American Indian who became acutely ill after returning from sea level during one of his several trips between Casapalca at 13 665 feet and Lima. Since then, 83 cases in all have been reported by Lundberg[3] Lizarraga[4] Bardalez[5] Alzamora-Castro[6] Hultgren and associates,[7-9] Stewart[1] and Fred and associates.[1] The Himalayan fighting of 1963 brought this disorder to India[11] and more than 430 cases have been recorded

Predisposing causes

Probably no age is exempt Many of the cases previously recorded were in children and young adults and the oldest patient was 4? years of age The Indian cases were in men between 18 and 53 years of age

Local residents and plainsmen who have stayed at an altitude above 11 000 feet for more than 8 months are not prone to attacks of high altitude pulmonary edema But if they return to high altitude after staying a few days at sea level they are unusually susceptible to it After they have stayed away at sea level for 6 to 12 months, the increased susceptibility disappears. They are then only as prone as the unacclimatized plainsmen to develop high altitude pulmonary edema

The vulnerable altitude varies from country to country and apparently depends on the snow line It is about 8 000 feet in the continental United States, 11 000 feet in the Himalayas, and 12 000 feet in the Peruvian Andes.

An individual's chances of developing pulmonary edema diminish rapidly after the third day of his arrival at high altitude and become remote after the tenth day Reinductees are prone to develop it earlier than others. The time lag between arrival and onset in such cases in the Peruvian Andes was 9 to 36 hours

Rapidity of arrival from a low to a higher altitude predisposes one to high altitude pulmonary edema It is not unusual to see pulmonary edema develop in an individual who has traveled by air A less fast journey but one associated with physical exertion may do likewise Pulmonary edema is not entirely confined to individuals moving beyond the vulnerable heights. Some cases may occur in persons on the way down from a high to a lower altitude. In such individuals and in those who develop pulmonary edema after more

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than a 10-day stay at high altitude physical exertion and exposure to cold are important contributing causes. In some individuals, however the protective reserve is only marginal and pulmonary edema develops even at rest. In fresh inductees, severe physical exertion on arrival at high altitude makes them as susceptible to high altitude pulmonary edema as the reinductees and the incidence in both is then the same

Clinical features

Characteristically high-altitude pulmonary edema begins with progressive cough and dyspnea. Cyanosis appears on the face and extremities, and râles are heard in the chest. There is no symmetry about the râles. They first appear on one or both sides in the interscapular area and spread to the upper zones. Both pulse and respiratory rates are increased. Tachycardia however is comparatively milder than dyspnea. In the early stages the lung bases are usually spared and the patient responds rapidly to oxygen therapy or evacuation to altitudes below 4 500 feet.

In fulminating cases the patient feels choked and wheezes are heard all around. He rapidly becomes moribund and hemorrhagic pleural effusions may occur on one or both sides before death

The onset may be less spectacular. In an individual afflicted with acute mountain sickness, increasing malaise, dyspnea or a dry cough are indications of impending pulmonary edema. In some cases, premonitory malaise, weakness pain in the calf muscles headache insomnia anxiety and excitement are followed by dyspnea and dry cough with or without palpitation before a full fledged picture of pulmonary edema becomes manifest. Dyspnea at night at rest on slight exertion for 1 to 3 days during which the man continues to be active may appear to be insignificant until pulmonary edema truly sets in. There may be frequency of micturition and oliguria.

Sometimes, cerebral symptoms dominate the picture. Giddiness, hallucinations, and lack of interest in surroundings lead to unconsciousness and pulmonary manifestations within a day or two

When the course is prolonged to 3 or 4 days or more clinical evidence of right ventricular failure such as distended neck veins, enlarged and tender liver and peripheral edema may be found

Early interscapular involvement and spread to the upper zones and absence of toxemia distinguish pulmonary edema from infection of the lungs. High fever leukocytosis, and increased blood sedimentation rate are usually absent. Moderate fever and leukocytosis occur *pari passu* with pulmonary edema and run the same course when the individual is treated with oxygen or evacuated to sea level. No antibiotics are required unless infection becomes superadded

Chest x ray films show pulmonary densities, usually first confined to the middle and upper zones, more predominant on the right than on the left side. In cases of slow onset interlobal septal lines indicative of interstitial edema may be seen. In severe cases, especially when prolonged over 2 or 3 days, all zones may be involved and there may be pleural effusion on one or both sides. In addition there is fullness of the hilar blood vessels, and the pulmonary artery is often and sometimes grossly enlarged. The rest of the configuration of the heart is not changed unless there is associated right ventricular failure in which case it becomes globular. On evacuation of the patient to sea level the pulmonary densities disappear in 6 to 48 hours but regression of the pulmonary artery may take 2 to 6 weeks.

The electrocardiograms show evidence of right axis deviation clockwise rotation T inversion in Leads V_1 V_2/V_3 prominent R in Leads aV_R V_1 and V_{3R}/V_{4R} and peaked P in severe cases. One or more of these changes may be present in milder cases. Evidence of myocardial ischemia without injury may be present in limb leads. Most of these changes reflect the degree of pulmonary hypertension concomitantly present with pulmonary edema and like the radiologic findings, take 2 to 6 weeks to disappear. As the inverted T waves revert, they may become abnormally high in most of the V leads and remain so for some time before becoming normal

In hemodynamic studies of convalescents, the pulmonary blood volume is found to be increased[13] and remains so for 3 to 24

weeks after evacuation of the patient to sea level

Necropsy findings

The macroscopic findings are characteristic of pulmonary edema, comparable in distribution with the clinical or radiologic findings. The right side of the heart is distended with blood and the left side is empty. All viscera are congested.

Microscopically, there is enormous distention of the pulmonary blood vessels as far as the capillaries. Scattered foci of hemorrhages are seen in the alveoli, as well as in the pleura. A remarkable feature is the extensive plugging of alveolar capillaries with sludged red blood cells. These plugs of sludged red blood cells are also seen in some of the thin walled veins. There is fibrinous exudate in the alveoli, some of which may be lined by a hyaline membrane akin to that seen in hyaline membrane disease. There are focal areas of atelectasis, and it is noteworthy that maximum capillary sludging is seen in these foci. With the PTAH stain[14] homogeneous or indistinctly laminated hyaline thrombi are seen in alveolar capillaries and some branches of the pulmonary artery. Similar fibrin thrombi are found in the kidney, plugging the glomerular and peritubular arteries, and also in the sinusoids of the liver.

Pathogenesis

Hemodynamic studies made within 12 to 72 hours of the episode in 5 cases have not revealed any evidence of left ventricular failure in high-altitude pulmonary edema. The left atrial and the pulmonary venous pressures were *normal*.[1] Therefore, for pulmonary edema to be precipitated hypoxic vasoconstriction must occur primarily or predominantly at the pulmonary venular level. Pulmonary edema would then be confined to areas of increased capillary pressure where the abundant transudate overloads the pulmonary lymphatics and escapes into the alveoli, hence the patchy densities seen in chest x-ray films. In experimental subjects there is a preferential lower zone vasoconstriction of greater or lesser magnitude in response to induced alveolar hypoxia. In the remaining zones the blood flow is increased. The patchy densities noted radiologically in high altitude pulmonary edema are identical in distribution and intensity to the increased areas of blood flow noted in these experiments.

The underlying mechanism of these vascular changes is not clear. But any explanation must take into account the fact that pulmonary edema does not occur immediately on arrival at high altitude but only after a delay of several hours. This rules out the direct effect of hypoxia or its indirect effect via the aortic and carotid reflexes, on the pulmonary circulation. It is interesting to note that lesions in the preoptic region result in lung hemorrhage and edema only after 1 to 24 hours.[14] It is possible that the effects of hypoxia in high-altitude pulmonary edema are mediated via the hypothalamus. If this should be the case, there will then be constriction of the venous reservoirs, and an excess volume of blood will be dumped into the pulmonary circuit, and pulmonary edema may occur.

The hypothalamus may be triggered into action by low arterial oxygen saturation or by constriction of cerebral blood vessels induced by a low CO_2 partial pressure (PCO_2). There is, however, a third possibility. The fact that the majority of individuals with high altitude pulmonary edema also suffer from acute mountain sickness may be significant. Symptoms of acute mountain sickness are aggravated by orally administered sodium bicarbonate[22] and appear to be due to respiratory alkalosis. Alkalosis induced by hyperventilation continues to increase in the early stages of acclimatization[1] and persists for weeks and months before renal excretion of bicarbonate eventually restores the blood pH to normal.[8-11] Alkalosis makes hemoglobin desaturation more difficult and tends to promote tissue anoxia,[22] which may not only adversely affect the hypothalamic mechanism but also predispose locally to pulmonary venous spasm. This may well account for the predisposition to pulmonary edema not earlier than 9 hours after arrival at high altitude and during the subsequent stay of several weeks at high altitude.

When acclimatized individuals move to sea level, there is a considerable destruction of red blood cells within 3 or 4 [illegible]

the plasma volume increases at the same time.[7] Arrival at high altitude is followed within a day by a decrease in plasma volume.[73] Before an adequate decrease occurs, however, the reinductee is highly susceptible to pulmonary edema within the first few hours of arrival at high altitude.

Physical exertion, particularly in snow, precipitates pulmonary edema by increasing the flow of blood and the activity of the right ventricle and by aggravating hypoxia with all of its consequently adverse effects at various levels.

In the Peruvian Andes, the incidence of pulmonary edema is high during the month of January, when the weather is especially favorable for the formation of ozone. And concentrations of ozone which are not in themselves sufficient to produce irritation and edema of the lungs diminish the uptake of oxygen.[74] This and other local environmental factors, such as hydrogen sulfide and heated or very cold air, may possibly account for restricted pockets of high altitude pulmonary edema at almost identical altitudes.

Several factors may be responsible for the associated pulmonary hypertension. Passive pulmonary hypertension is nearly always present, resulting from increased capillary pressure. Active pulmonary hypertension may occur as the result of powerful reflex vasoconstriction of the arterioles and venules due to hypoxic stimulation of the carotid and aortic bodies.[75] The effect may be facilitated by increased sensitivity of the single muscle cells present in the walls of the arterioles and venules[76] to low oxygen tensions, by local release of catecholamines,[77] and probably by failure of the hypoxic lung to inactivate serotonin.

The persistence of pulmonary hypertension for weeks after pulmonary edema has subsided is an indication, however, that the changes induced in the pulmonary circulation are not entirely functional. The sludging of cells and the fibrin thrombi in the alveolar capillaries and venules add an organic element to the picture. These findings suggest that exposure to hypoxic stress causes a breakdown of the fibrinolytic enzyme system, and the equilibrium between fibrin formation and dissolution is upset.

Treatment

The vast majority of individuals afflicted with pulmonary edema respond either to oxygen therapy given locally or to evacuation to sea level. This happens in spite of the fact that inhalation of 100 per cent oxygen by the BLB mask may not correct completely the arterial hemoglobin desaturation even in healthy individuals.[11] The response, if it is to occur, is always quick. Lack of response may be due either to functional hypoventilation or to the presence of organic changes, such as obstruction of blood vessels, atelectasis, and alveolar fibrin membranes. On acute exposure of the patient to lower ambient oxygen tension, the carotid and aortic chemoreceptors are stimulated and ventilation is increased. The resulting fall in PCO_2, however, depresses the pH of the cerebrospinal fluid, which in turn reduces the neural activity of the medullary respiratory pH receptors. The effect of carotid and aortic chemoreceptor stimulation is, therefore, partially neutralized, and as long as the pH of the cerebrospinal fluid is not restored to normal, an increase in ventilation does not occur to the full extent.[78] In addition, alkalosis decreases the intensity of the anoxic stimulus of the carotid and aortic chemoreceptors. When functional hypoventilation is present due to the altered cerebrospinal fluid pH, oxygen administered by intermittent positive pressure respiration is helpful. When, however, organic changes are present, hyperbaric oxygen is possibly needed.

Patients suffering from high-altitude pulmonary edema tolerate morphine well and it can be used with impunity to allay anxiety and restlessness. Many patients make remarkable improvement after its use. The beneficial effect of morphine appears to be due to a redistribution of blood to the periphery. The pulmonary blood volume is thereby lowered[13] and pulmonary edema is relieved. Atropine, aminophylline, and digoxin, which normally lower the central venous pressure, are probably useful adjuvants.

Reinductees with increased blood vol-

ume who develop high-altitude pulmonary edema during the first 3 days of arrival before the blood volume begins to fall may benefit from rapidly acting diuretics, such as Frusemide or ethacrynic acid.

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Clinical communications

Ideal isolated levocardia

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Levocardia with situs inversus is a rare condition in which complete or partial situs inversus of the abdominal viscera is associated with a heart that occupies its normal position. It has been estimated to occur in approximately 1 per cent of all cases of congenital heart disease,[1,2] being associated in most instances with complicated cardiac malformations. Seventy-five per cent of patients with levocardia do not survive the first year of life and only 6 per cent are alive at the end of 5 years.[3] The poor prognosis is related to the frequent occurrence of severe cyanotic heart disease. Atrial septal defects, ventricular septal defects, and endocardial cushion defects are quite common and frequently are associated with transposition of the great vessels, truncus arteriosus, pulmonary stenosis, anomalous systemic or pulmonary venous drainage, or other complicated cardiac anomalies. So rare is a simple cardiac defect or a normal heart in a patient with levocardia that precise demonstration and documentation is required before such a diagnosis can be accepted.

Of more than 160†[1,4-44] cases of levocardia with situs inversus or heterotaxy of the abdominal viscera which have appeared in the literature, 9‡ may be considered to be probable examples of a normal heart with no significant abnormality of cardiovascular hemodynamics. The latter group includes reports of single necropsied cases by von Hoffman[7] in 1887, Toldt[8] in 1889, Caveda Colomé[9] in 1945, Charache[10] in 1942, Tanner-Cain§[11] in 1951, and Ivemark[4] in 1955, and 3 clinical case histories

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†Although no attempt was made to include all such cases which have been reported in the foreign literature, we have sought to compile an accurate bibliography of those cases which have appeared in the English literature plus those cases written in foreign languages about which adequate facts were available. Cases in the foreign literature were accepted as examples of this anomaly when sufficient information was available to us from abstracts, when they were adequately described in an English review article, or when the title specified the presence of levocardia and situs inversus viscerum. Since in many instances a single case has been reported separately by two or more authors, we have tried to record each case only once in our bibliographic compilation. The figure used above was obtained by a search of the English literature from 1952 through 1963, and by adding all previously unreported cases cited in the better reviews on this topic published prior to 1954 (see Table I).

‡Although Thomson[illegible] mentions 4 cases[illegible] as examples of levocardia with situs inversus viscerum in which the heart was reportedly normal, Gelpel's[illegible] Case No. 2 is incorrectly included as one of this group, and in the other 3 cases the information about the heart in the original articles is insufficient to exclude cardiac abnormality.

§Although the heart was not "normal" since a thickened endocardium and an enlarged heart were reported, no congenital derangements of structural or anatomic relationships were noted.

published by Gibert-Queraltó[12] in 1960, Taussig[13] in 1960, and Rosenbaum*[14] in 1962. Of these 9 cases, only the 2 published in 1960 by Gibert-Queraltó and by Taussig provide relatively complete clinical information about the heart, including physical findings, electrocardiograms, and x-ray films. Cardiac catheterization was included as a part of the clinical investigation only in Taussig's case and revealed normal hemodynamics and normal venous angiogram. However, the point of entrance of the inferior vena cava into the right atrium was not demonstrated and the cardiac contour was abnormal.

Although levocardia with heterotaxy of the abdominal viscera and a completely normal heart is apparently a rare occurrence, the exact incidence of this condition is probably greater than indicated by the few cases recorded in the literature, since it seems likely that some such cases are not recognized by the clinician. Nevertheless, because of the infrequency of occurrence and/or recognition of this entity, and because it is the first case completely documented by cardiac catheterization and angiocardiography, we are reporting the findings in a Negro female with this anomaly.

Case report

F. J. W. (John Gaston Hospital #143663), a 16-year-old Negro girl, was seen in the Cardiovascular Clinic in June, 1963, for evaluation of a heart murmur. Birth and developmental history had been normal, but on the basis of a preschool examination at the age of 6 she had been informed of the presence of a "weak heart." When 10 years old she developed migratory polyarthritis which necessitated her hospitalization. On admission, a soft systolic murmur was described in the second left intercostal space and a soft blowing systolic murmur was heard at the apex. Radiologic evaluation of the chest revealed a heart of normal size with no observed abnormality. Serial electrocardiograms revealed a notched, low-voltage rs pattern in Lead V₁ with normal intrinsicoid deflection and were considered to be within normal limits (Fig. 1A). Hematocrit, throat culture, ASO titer, sickle cell preparation, serum electrolytes, and urinalysis were all normal. White blood cell count was 17,500 per cubic millimeter, with 81 per cent neutrophils. C-reactive protein was 3+, and sedimentation rate was 30 mm. per hour. The clinical impression was active rheumatic fever with carditis. After treatment, which included steroids, she rapidly became asymptomatic, although a systolic precordial cardiac murmur remained. The tentative diagnosis of rheumatic carditis then led to the institution of a program of penicillin prophylaxis which was continued for the next 5 years during observation in the Pediatric Clinic. She was asymptomatic throughout this period. Further medical history was not pertinent and specifically did not include a family history of congenital heart disease.

Significant findings on physical examination of this apparently healthy Negro girl were limited to the cardiovascular system. A blood pressure of 118/78 mm. Hg and a regular pulse rate of 72 per minute were present. All arterial pulses were palpable and of normal amplitude. The heart size was normal, with the apical impulse in the fifth left intercostal space medial to the mid-clavicular line. There was a Grade 3/6 medium-pitched ejection type of systolic murmur that was heard best at the second and third intercostal spaces at the left sternal border. The murmur was also audible at the apex and high in the left axilla. The first and second heart sounds were normal, with normal respiratory splitting of the second sound.

The initial clinical impression was acyanotic congenital heart disease, the murmur most likely resulting from pulmonary stenosis. However, because of the history of rheumatic fever and because of situs inversus with levocardia, cardiac catheterization was deemed to be advisable. During hospitalization for this procedure the following additional laboratory examinations were reported to be normal: hematocrit, total and differential white blood cell counts, urinalyses, serum electrolytes, ASO titer, C-reactive protein, protein-bound iodine, sickle cell preparation, and a lupus erythematosus preparation. Blood smears revealed no Heinz or Howell-Jolly bodies. An electrocardiogram (Fig. 1B) revealed a sinus mechanism with sinus arrhythmia. P waves were upright in all leads. QRS complexes were considered to be within normal limits, and T waves were inverted in Leads V₁ and V₂. A multiview roentgenographic cardiac examination revealed a heart shadow of normal size with the stomach on the right side (Fig. 2). No specific chamber enlargement or valvular calcification was seen.

Cardiac catheterization demonstrated no hemodynamic abnormality. The right side of the heart was entered normally through the right basilic vein via a normal superior vena cava. Normal intracardiac pressures and oxygen saturation values were obtained (see Table II). A systolic pressure gradient of 5 mm. Hg across the pulmonary valve when the catheter was withdrawn from the pulmonary artery was not considered to be significant. Cineangiocardiography demonstrated no abnormality of the pulmonary arterial tree, pulmonary veins, left atrium, left ventricle, or aorta. Left-sided cardiac catheterization by the percutaneous retrograde approach through the femoral artery demonstrated

*The diagnosis of levocardia with situs inversus viscerum was made by Rosenbaum in his Case No. 3 on the basis of a chest x-ray film that showed a normal cardiac shadow and right-sided gastric air bubble. Except for the recording of an electrocardiogram, which was normal, no further studies were made in this case and the author himself notes that the diagnosis is presumptive.

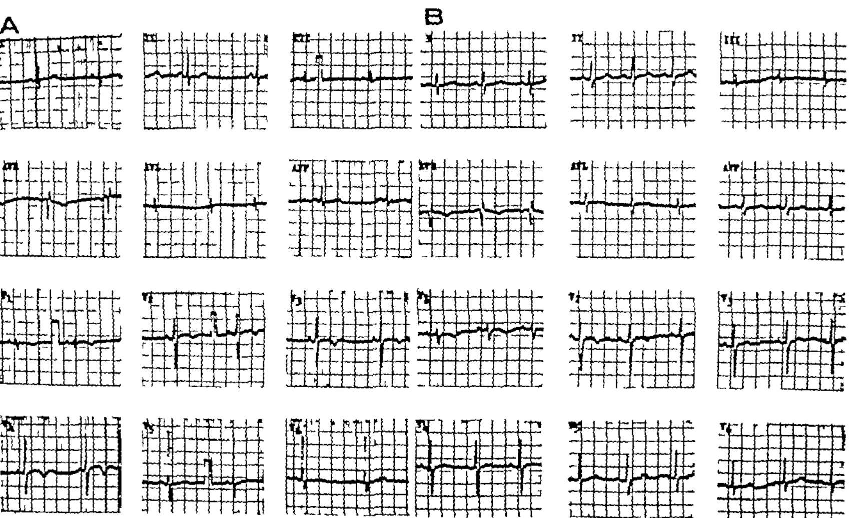


Fig. 1. *A*, Electrocardiogram recorded at 10 years of age when patient was hospitalized for suspected acute rheumatic fever. Note the notched R in Lead V[illegible] and the juvenile T wave inversion pattern in Leads V[illegible]. *B*, Recent electrocardiogram recorded when the patient was 16 years old shows less notching of QRS in Lead V[illegible] and loss of T wave inversion in Leads V[illegible].

Table I. Eighty-eight cases of isolated levocardia cited in selected review articles

Forgacs 1947	*Campbell and Forgacs 1953*	*Ivemark 1955*		*Putschar 1954*
1. Hickman, 1869 2. Marchand, 1883 3. Griffith, W., 1897 4. Lochte, 1898 5. Geipel, Case No. 3, 1899 6. Hingst, 1901 7. McCrae, 1905 8. Royer, 1908 9. Knape, 1912 10. Shaw, 1924 11. Miller, 1925 12. Author Case No. 1 13. Author Case No. 2	1. Hardy, Case No. 2, 1948 2. Del Carril, 1949 3. Robinson, 1950 4. Thomson, Case No. 1, 1950 5. Thomson, Case No. 2, 1950 6. Tanner-Cain, 1951 7-13. *Young, 1951 14-18. Doliopoulos, 1952 19-26. †Author	1. Martin, 1826 2. Epstein, Case No. 2, 1886 3. Lawrence, 1901 4. McLean, 1922 5. Pernkopf, Case No. 4, 1926 6. Hu, 1929 7. Toodury, 1936 (Fuetter, 1938) 8. Roseman, 1942 9. Weinberg, 1949 10. Lefkin, 1951	11. Polhemus, Case No. 1, 1952 12. †Polhemus, Case No. 3, 1952 13. Polhemus, Case No. 4, 1952 14. Boggs, Case No. 1, 1953 15. Baumann, Case No. 2, 1954 16. Bush, 1955 17-28. Author Cases Nos. 2, 4, 5, 7, 8, 9, 11, 12, 13, 15, 16, and 17	1. von Hoffman, 1887 2. Toldt, Case No. 1, 1889 3. Pernkopf, Case No. 5, 1926 4. Charache, 194[illegible] 5. Caveda Coloné, 1945 6. Conn, Case No. 4, 1950 7. Gasser, Case No. 2, 1952 8-11. Author Cases Nos. 1, 2, 3, 4
Remarks	*Remarks*	*Remarks*		*Remarks*
Numbers 1-11 above are autopsied cases; 12 and 13 are clinical cases. Brechet's Case No. 2, 1826, although cited by several authors as a case of levocardia, did not describe the position of abdominal viscera and has been omitted by us.	Cases above which were autopsied are those of Robinson, Tanner-Cain, Young Case No. 2, Doliopoulos Cases Nos. 1 and 3, and the author's Cases Nos. 1, 7, 8, and 9. *Case No. 1 of Young was reported by Tanning in 1947 and is omitted here. †Author Case No. 14 was reported by Forgacs in 1947 and is omitted here.	All autopsied and all with asplenia, except author's Cases Nos. 15, 16, and 17 which had splenic anomalies. No cases included by Forgacs or Campbell and Forgacs are included here. *Not considered to have situs inversus by Putschar although the liver was transposed and the stomach was not rotated to the left. †Not considered to have situs inversus by Putschar although patient had symmetrical liver and midline gallbladder.		All autopsied cases. No cases from the other 3 review articles used in this table are included here.

normal left ventricle and aorta and showed no evidence of mitral insufficiency on cineangiocardiograms recorded during pressure injection of contrast medium into the left ventricular chamber. Left ventricular and aortic pressures were normal, and no abnormalities in the anatomic relationships of these structures were present. Injection of radiopaque contrast medium into the inferior vena cava demonstrated normal drainage of this vessel into the right atrium. A venogram revealed that the left innominate vein emptied into the superior vena cava normally, thus excluding the presence of a persistent left superior vena cava. A small abdominal aortogram demonstrated normal renal arteries and normal-sized kidneys and the spleen in the right upper quadrant (Fig. 4). The liver and gall bladder were located more medial than usual, as demonstrated by a liver scan with [illegible]

I[131]-labeled rose bengal and by oral cholecystography, respectively. Barium enema (Fig. 4) showed the entire colon to be in the right half of the abdominal cavity.

Discussion

In addition to being a rare congenital anomaly, levocardia with complete or partial situs inversus is also frequently associated with absence of the spleen. This latter relationship is well documented by Ivemark[3] and Putschar[4] in their reviews on splenic agenesis and other splenic anomalies associated with congenital cardiac malformations. Of the 78 [illegible]



Fig. 2. Roentgenogram of chest. Posterior-anterior view after barium swallow reveals normal cardiac size and contour and the stomach lying in the right upper quadrant of the abdomen.

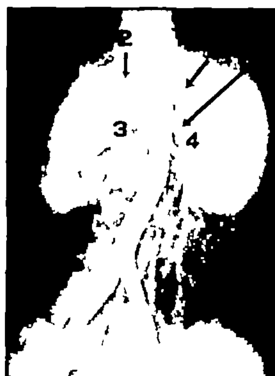


Fig. 3. Aortogram of abdominal aorta. *1*. Splenic blush in right upper quadrant. *2*. Splenic artery. *3* and *4*. Right and left renal arteries. *5*. Superior mesenteric artery. *6*. Large artery which probably supplies part of the medially situated liver.

Table II. *Cardiac catheterization data*

Observation sites	*Blood oxygen content* (*ml./100 ml.*)	*Blood oxygen saturation* (*%*)		*Intravascular pressures* (*mm. Hg*)	
		Van Slyke	*Oximeter*	*Phasic*	*Mean*
Superior vena cava			83	8/4	6
Right atrium			81	9/3	6
Right ventricle			81	23/0–4	8 5
Pulmonary artery	10 4	75	80	20/7 5	13
Left ventricle				122/0–11	43
Ascending aorta	13 2	94	97	127/82	115

Oxygen consumption (ml./min.) 217
Systemic blood flow (L./min.) 7 8
Cardiac index (L./min./M.²) 5 0

*Waters oximeter not calibrated for precise correlation with Van Slyke saturation determinations.



Fig. 4. Barium enema. All of the colon lies to the right of the midline, except for the cecum, which is seen to lie behind the descending colon and slightly to the left of the midline.

cases of asplenia which Putschar records, 23 are thought to be cases of levocardia with total or partially transposed abdominal viscera. Ivemark also includes data on 3 cases in which levocardia and visceral inversion were associated with other splenic anomalies. Although most patients with levocardia and partial abdominal situs inversus have associated splenic agenesis, the present case does not fall into this category. In addition to demonstration of the splenic "blush" on the aortogram, absence of Howell-Jolly and Heinz bodies in the patient's blood smear was established.

Levocardia with abdominal visceral heterotaxy is quite analogous to isolated dextrocardia, the latter term being applicable when the heart occupies the right side of the thorax, whereas total situs inversus of abdominal organs is lacking. Like the incidence of the former, that of isolated dextrocardia is low, yet the types and combinations of associated cardiac defects which occur in the two conditions are very similar.[19,44] Adequate reviews have appeared in the literature recently which classify cases of levocardia with situs inversus according to differences in anatomic arrangement of cardiac chambers (mainly the atria) and which detail the types of associated cardiac defects present in such cases.[1,41,48]

Individuals having levocardia and abdominal heterotaxy in which the heart is essentially normal are apparently extremely rare. The incidence of such cases is probably greater than indicated by the number reported, since suspicion of this diagnosis would be unlikely in the presence of a normally placed heart unless a right-sided gastric air bubble or situs inversus of the gastrointestinal tract were noted on appropriate x-ray films. Nevertheless, the sparsity of such reported cases does not seem to represent a simple lack of recognition clinically. If such were true, the incidence of this entity noted at routine postmortem examinations would be much higher.

In the case of levocardia with a normal heart the cardiac chambers maintain their usual anatomic relationship and thus fall into Group I of Shaher's[39] classification in which normal atrial anatomy is preserved. The frequent persistence of a left superior vena cava, the common occurrence of anomalies of venous drainage from the lower part of the body, and the possibility of anomalous pulmonary venous drainage require cardiac catheterization and appropriate angiocardiography for a precise antemortem diagnosis of a "normal" heart.

When the left superior vena cava does not persist, thus leaving a single, normal right superior vena cava, the aortic arch usually descends on the left. Cineangiocardiography in this patient confirmed the presence of normal anatomic arrangements of the superior vena cava and the aorta. Moreover, the normal positions of the superior vena cava and the atria were suggested prior to angiocardiography by the finding of an upright P wave in Lead I of the electrocardiogram, since there is usually inversion of the P wave in this lead in cases in which the superior vena

cava and the venous atrium lie on the left side of the heart.[4,17,18] Such P wave abnormalities are not a consistently reliable criterion of atrial orientation because of similar changes resulting from nodal rhythm or atrial disease and because nodal rhythm is common in levocardia with corrected transposition.[14]

Of the 9 reported cases which have been accepted as probable or proved instances of this rarely recognized phenomenon, 5 represent autopsy reports, and only 1 of the other 4 was studied clinically by electrocardiography, roentgenography, and cardiac catheterization. The case reported here is only the second recorded of a living individual in whom isolated levocardia without cardiac abnormality was adequately substantiated by appropriate objective studies. Although our patient has a systolic murmur at the base of the heart which resembles that of pulmonary stenosis, no alterations in cardiac hemodynamics were demonstrable by cardiac catheterization, and cineangiocardiography of both sides of the heart and adjacent vessels was normal.

Summary

Levocardia with situs inversus, a rare congenital disorder, is usually associated with severe cyanotic congenital heart disease. Review of the literature reveals reports of over 160 cases, in only 9 of which were the hearts presumably normal, and this presumption was proved clinically in only 1 patient. The case presentation here recorded concerns an individual in whom cardiac catheterization, cineangiocardiography, and radiologic studies of the abdominal viscera demonstrated a hemodynamically normal left-sided heart associated with partial situs inversus viscerum. Normal spatial arrangements of the heart chambers and the great vessels were also verified in what is thought to represent a very rare example of ideal isolated levocardia in a 16-year-old Negro girl who is living and well.

A comprehensive bibliography on this unusual group of congenital malformations in man has been assembled.

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Complete heart block and the role of atrial activity

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The atrium has been studied by different methods, including auscultation, phonocardiography, electrocardiography, vectorcardiography, venous pulse tracings, apexcardiography, ballistocardiography, and electrokymography.

The information obtained by these methods is primarily concerned with hypertrophy and time relationships between atrial and ventricular contractions.

The booster effect of atrial systole on the filling of the ventricles has long been recognized[1,2,4-6] but more recent experimental work done in animals with surgically induced complete atrioventricular heart block has corroborated and extended the previous studies.[3,6,7]

The human subject with acquired complete heart block offers a means of analyzing (a) the contribution of the atrial contraction to the performance of the following ventricular contraction, and (b) the changes that will occur when a sympathomimetic amine is administered.

Material and methods

Ten patients with complete atrioventricular block due to arteriosclerotic heart disease were studied; 4 were women and 6 were men. The mean age was 70.6 years. Four of the cases were Grade I, 4 were Grade II, and 2 were Grade III according to the New York Heart Association classification. Four of the patients had had an infarction; the most recent one had occurred 2 years prior to the study.

An electrical pacemaker had been inserted into the wall of the left ventricle in all of the patients, and at the time of the study all of the patients were being regularly paced by the pacemaker at a rate of 62 to 75 beats per minute. Two patients, because of signs of heart failure, were on digitalis at the time of the study. All studies were performed with the patient in the horizontal position.

Ejection times were taken from the carotid tracing during halted expiration at a high paper speed (200 mm. per second) and a time line of 20 msec. Punctures of the brachial artery were performed and arterial pressure curves were recorded with a P23Db Statham strain gauge. The transducer was placed at the level of the right atrium. The length and internal diameter of the tubing from the needle to the transducer was 50 cm. and 0.08 inches, respectively. Precordial electrocardiograph electrodes were placed in the positions best for recording the P waves. Cardiac outputs were determined by the dye-dilution technique.

The first derivative of the arterial pressure curves was either calculated mathe-

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matically or more recently obtained by means of an R-C differentiating circuit.

In 4 patients, isoproterenol was given intravenously for 10 to 15 minutes at a constant rate of 2 micrograms per minute. Cardiac outputs, intra-arterial blood pressures and ejection times were determined at 2, 4, 8, 10 and 15 minutes during the administration of this drug. The figures shown in Table II were obtained before the administration of the drug and at the time of maximum increase in the cardiac output.

Results

Ejection time. The average ejection time achieved was 286 ± 17 msec. when the P-R interval was 100 to 250 msec. (optimum zone) (see Table I).

When the P wave of the electrocardiogram fell during the QRS complexes (basal zone), the average ejection time for the group was 250 ± 19 msec.

The absolute difference was 36 msec. which represents 12.5 per cent of the maximum ejection time. The statistical difference between these two groups is highly significant ($p < 0.001$).

Fig. 1 represents the changes in ejection time in one typical case. It is interesting to observe that when the atrial systole occurred during the T wave, it was still partially effective in prolonging the ejection time.

Arterial blood pressure. The average systolic and diastolic pressures during the "optimum zone" were 133 ± 19 and 64 ± 9 mm. Hg, respectively.

During the "basal zone," the average systolic pressure was 119 ± 20 mm. Hg and the average diastolic pressure was 62 ± 16 mm. Hg.

The absolute differences between the blood pressures for "optimum zone" and for "basal zone" were 14 and 2 mm. Hg for systolic and diastolic, respectively. The increments (in per cent) for the systolic and diastolic pressures given by the atrial activity were 10.5 and 3.1 per cent in each case (Table I).

The statistical difference for systolic blood pressures was highly significant

Table I. Contribution of the atrial contraction to ejection time, blood pressure, and peak first derivative of the arterial pressure

Patient	*Ejection time (msec.)*		*Blood pressure (mm. Hg)*				*Peak dp/dt (mm. Hg/sec.)*	
			Systolic	*Diastolic*	*Systolic*	*Diastolic*		
	100-250 msec.	*During QRS*	*100-250 msec.*		*During QRS*		*100-250 msec.*	*During QRS*
B.B.	290	263	134	62	121	60	813	650
P.L.	290	260	144	70	131	68	815	597
S.T.	290	257	145	68	135	63	855	652
S.E.	300	259	160	71	147	69	811	592
A.B.	272	242	125	58	110	58	870	690
R.T.	286	249	90	47	81	47	778	524
M.A.	255	206	135	75	108	66	880	539
O.L.	290	266						
B.M.	320	269						
A.A.	267	231						
Average	286	250	133	64	119	62	832	606
Standard deviation	±17	±19	±19	±9	±20	±16	±34	±48
Difference		36			14	2		226
Per cent change		12.5			10.5	3.8		27.1

Note: The numbers that appear in the tables in each case represent the average of multiple readings that fell in the same P-R interval zone.

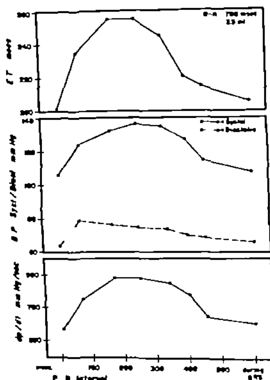


Fig 1 Ejection time systolic and diastolic arterial pressures, and peak positive dp/dt of the arterial pressure curve in one typical case The T wave in this case occurred between 400 and 490 msec

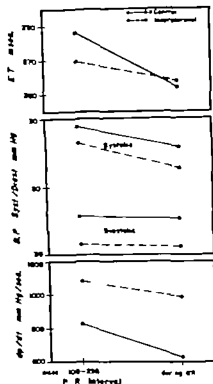


Fig 2 Ejection time, systolic and diastolic blood pressure and peak positive dp/dt during the two zones (100-250 msec and during QRS) of the P R interval before and during the administration of isoproterenol

($p < 0.001$) whereas the difference for diastolic pressures was not significant ($p < 0.1$)

It can be observed that atrial systole properly timed will contribute primarily to the increase in the systolic pressure. This measurement followed approximately the same pattern of ejection time when plotted against P R intervals (Fig 1)

Peak positive first derivative of the arterial pressure curve The peak positive dp dt was 832 ± 34 mm Hg per second during the "optimum zone" and 606 ± 48 mm Hg per second during the "basal zone" The absolute difference was 225 mm Hg per second which represents 27 1 per cent of the maximum peak dp dt The statistical difference is highly significant ($p < 0.001$)

Isoproterenol

EJECTION TIME The ejection time of the "optimum zone" fell from an average of 286 msec during the control period to an average of 269 msec during the administration of isoproterenol (Table II and Fig 2) The ejection times of the "basal zone" did not change significantly but actually rose from a control of 254 msec to 258 msec during administration of the drug It can be observed that the decrease in ejection time is due entirely to diminution of the atrial filling capacity In fact the atrial contribution dropped from 11 to 4 per cent of the corresponding maximum ejection times. The statistical analysis of the differences in ejection times between the two zones (optimum and basal) before and during the administration of isoproterenol gives a value of $p < 0.02$

ARTERIAL BLOOD PRESSURE Both the systolic and diastolic pressures fell with the infusion of the isoproterenol from a control value of 124 59 mm Hg to 109 38 mm Hg when atrial contraction occurred during the "optimum zone" and from a control of 112/57 mm Hg to 96/37 mm Hg when the atrial activity was at the "basal zone" (Table II and Fig 2)

Table II Changes in ejection time blood pressure and peak first derivative of the arterial pres

Patient	Ejection time (msec)				Blood pressure (mm Hg)	
	Before		During		Before	
	100-250 msec	During QRS	100-250 msec.	During QRS	100-250 msec	During QRS
B.B	292	255	280	270	134/62	121/60
T R	286	249	260	252	90/47	81/46
S.T	295	270	280	270	145/68	135/65
B A	272	242	255	240	125/58	110/58
Average	286	254	269	258	124/59	112/57
Difference		32		11		12/2
Per cent change		11		4		9 7/3 4

The percentage of atrial contribution to arterial pressures did not change before or during the administration of the drug It was 12 and 2 per cent for systolic and diastolic pressures, respectively during the control and 11 and 1 per cent during the administration of isoproterenol The p value resulting from a comparison of the differences in systolic pressures before and after isoproterenol is greater than 0 20 and also not significant for the diastolic pressure

PEAK POSITIVE FIRST DERIVATIVE OF THE ARTERIAL PRESSURE CURVE The peak dp/dt increased in both zones of the P R interval (Table II and Fig 2) During the control peak dp/dt was 829 mm Hg per second at the optimum zone and 629 mm Hg per second at the "basal zone representing an increase of 24 1 per cent.

When isoproterenol was given peak dp/dt values were 1 107 and 971 mm Hg per second in these two zones. The percentage of atrial contribution was only 12.2 per cent (Table II and Fig 2) Although there was a tendency of the gradient to decrease between the two zones before and during the administration of isoproterenol it was not statistically significant ($p > 0.20$)

As can be seen in Table II the stroke volume increased by an average of 53 per cent with administration of this drug

Discussion

The role of the atria as has been previously demonstrated is primarily that of increasing the filling of the ventricles[2,3,4,7] and of setting the A V valves in a semi-closed position at the beginning of ventricular contraction [9]

It is believed that venous return is a result of three main forces a passive vis a tergo a possible active vis a fronte that occurs during systole and an early diastole[9,10]— sucking action of the ventricles, and finally active atrial contraction.

There is no reason to believe that the first two factors just mentioned did change significantly Consequently it is inferred that the changes in the different parameters are due to different timings of the atrial contractions

As can be seen in Fig 1 the correct timing of atrial systole results in clear prolongation of the ejection time and increase in systolic pressure and peak dp/dt

When the atrial contraction fell during the T wave (Fig 1) it was still partially effective in increasing the above-mentioned parameters.

This could sound illogical since the A V valves are closed during the T wave and the atrial action would be expected to be ineffective. However It is known that the interval from the beginning of the P wave

sure before and during the administration of isoproterenol

Blood pressure (mm. Hg)		*Peak dp/dt (mm. Hg/sec.)*				*Stroke volume (ml.)*	
During		*Before*		*During*		*Before*	*During*
100-250 msec	*During QRS*	*100-250 msec.*	*During QRS*	*100-250 msec*	*During QRS*		
126/40	122/38	813	650	1240	1143	55	99
89/38	80/38	778	524	781	630	74	91
105/35	98/34	855	652	1102	1029	56	97
115/40	85/38	870	690	1305	1082	57	80
109/38	96/37	829	629	1107	971	60	92
	11/1		200		135		
	10/2 6		24 1		12 2		

of the electrocardiogram to the end of the a wave in an atrial pressure tracing varies from 170 to 240 msec.[3] and this may explain this late and partial contribution.

A P wave falling during the QRS complex does not add anything to the following ventricular contraction. In fact, it is conceivable that it will produce a slight regurgitation through the A-V valve.[7]

Ejection time, pressure and peak dp/dt are higher during the optimum P-R interval, probably because the semi-closed position of the mitral valve at the time of ventricular contraction gives a steeper rise in ventricular pressure. In other words, it would take less time for the ventricles at the beginning of the systole to close an already semiclosed mitral valve. This has been observed previously by Siecke and Essex[3] in dogs with surgically induced complete A-V block. As a matter of fact, the A-V pressure difference is negative at the onset of ventricular systole for P-R intervals of 100 to 300 msec. favoring a partial closure of the A-V valves.

Animal studies on the booster action of the atrium have demonstrated that the aortic flow is significantly increased by the proper timing of the atrial contraction.[7] It is possible then that the increase in stroke volume occurs as a result of synchronous atrial activity. This would explain the present findings of increased ejection time, systolic and diastolic pressures, and peak dp/dt on the basis of increased distention of the fiber length. The rise in blood pressure should then be considered to be a result of increased output against an unprepared peripheral resistance.

The hemodynamic response to the administration of isoproterenol that is supposed to act in the beta receptors[13,20] has been extensively studied. It has been proved to increase contractility and cardiac output and decrease systolic ejection time and peripheral resistance.[11-14,18]

Peak dp/dt from the ventricular pressure curve has been observed to increase significantly with the administration of isoproterenol.[17]

These data show that atrial systole during the administration of isoproterenol is proportionately less effective in prolonging ejection time. However, its effect in elevating the systolic pressure is maintained. Peak dp/dt gradient between the two zones showed a tendency to decrease after the administration of the drug.

This is most likely due to a significant diminution of myocardial compliance and, therefore makes the filling function of the atrium more difficult. This is probably not due to increased venous pressure since isoproterenol on the contrary de-

creases venous pressure.[9,14] The fact that the relationship of mean left atrial pressure to left ventricular end-diastolic pressure is independent of changes in stroke volume and aortic pressure[15] also rules out these factors as determinants of this relative insufficiency of the atrium during infusion of isoproterenol.

Indirect evidence of the increased work of the atrium during the administration of isoproterenol comes from the electrocardiographic changes observed with this drug. There is an increase in the amplitude of the P wave and augmentation of the auricular gradient by increasing T.[18]

Summary

Ten patients with complete atrioventricular block were studied in order to evaluate the contribution of the atrial contraction to the following ventricular contraction. Ejection times, intra-arterial blood pressures, and peak dp/dt were measured.

These data indicate that proper atrial timing produces a considerable increase in ejection time, systolic arterial pressure, and peak positive dp/dt.

Administration of isoproterenol resulted in a substantial decrease in ejection time only when atrial systole occurred at the proper time, but no change was observed before and during the administration of isoproterenol when the atrial systole was not synchronous. Systolic and diastolic pressures decreased during administration of the drug, and the contribution of the atrium was maintained. Peak positive dp/dt rose in both zones of the P-R interval, and the atrial contribution slightly decreased. The conclusion is that isoproterenol decreases myocardial compliance, and the action of the atrium is diminished proportionately.

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Effect of triamterene on elevated arterial pressure

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An effective oral diuretic which reduces blood pressure but conserves potassium would have obvious advantages over currently available agents. Triamterene (2 4 7-triamino-6-phenyl pteridine) is an oral diuretic whose action is distinct from that of the aldosterone antagonists and the benzothiadiazines. Like spironolactone triamterene causes loss of sodium and retention of potassium and initially was believed to be an aldosterone antagonist. Subsequently however it was shown to increase the urinary output of sodium in adrenalectomized animals[3] and appears to have a direct effect upon tubular exchange mechanisms. The natriuresis without loss of potassium produced by triamterene is a desirable feature in a hypotensive agent which must be administered daily for years. Therefore, we have compared the effect of triamterene upon the blood pressure of hypertensive patients with that of chlorthalidone an oral diuretic of known hypotensive value The effect of the two agents separately and together on blood pressure and on concentrations of serum urea, creatinine potassium and uric acid has been observed in a double blind crossover trial

Methods

Observations were made on 5 men and 6 women 42 to 61 years of age (Table I) One woman was known to have chronic pyelonephritis, on radiologic and bacterial evidence and one had recurrent attacks of infection of the urinary tract without radiologic evidence of renal disease and with a normal level of blood urea the latter patient also had a strong family history of hypertension. No cause of hypertension was found in the other patients. All the patients had moderate elevations of blood pressure without retinal hemorrhages or exudates, except Patient K who had severe hypertension retinal hemorrhages, and exudates. This patient had previously shown satisfactory control of the blood pressure with guanethidine and poor control with methyldopa but had refused further treatment with either of these drugs because they caused failure of ejaculation One other patient had been treated previously with oral diuretics and

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Table I Mean levels of blood pressure and other variables for each patient during the control period

Patient	Age (yr)	Sex	Renal disease	Blood pressure (mm Hg)		Blood urea (mg./100 ml)	Plasma potassium (mEq./L.)	Plasma creatinine (mg/100 ml)	Plasma uric acid (mg./100 ml)
				Lying	Standing				
A	45	M	–	187 7 125 2	182 3/129 8	40	4 4	1 00	5 30
B	61	F	–	160 3/ 99 5	149 8/101 0	37	3 6	1 34	4 13
D	47	M	–	156 0/103 0	147 9/104 9	34 3	3 6	1 33	4 56
E	49	F	+	212 3/118 5	203 5/118 0	26	3 8	1 21	3 8
F	54	F	–	192 5/109 7	187 7/119 8	39	4 3	1 52	4 28
G	43	F	+	174 8/ 99 2	166 8/101 7	37	3 3	1 00	3 5
H	49	M	–	182 3/118 2	179 5/123 0	39	3 8	1 36	4 80
J	51	F	–	157 0/ 85 7	162 3/ 92 0	49	3 6	1 24	4 57
K	42	M	–	206 3/136 3	215 3/141 3	30	3 6	1 64	—
L	51	F	–	231 3/114 0	227 0/109 3	34	3 6	1 60	3 8
M	51	M	–	188 3/118 0	189 0/127 7	28	3 7	1 51	—

one with reserpine The remainder of the patients had not been treated previously None had clinical evidence of cardiac failure at the time of the trial. All the patients carried on their ordinary work without restriction of diet or exercise.

Each patient was seen at weekly intervals for 27 weeks. At each visit the patient was weighed and the arterial pressure was measured by sphygmomanometry with the patient standing and lying Every fortnight blood was drawn for estimation of urea (by Autoanalyzer) uric acid[9] potassium (by flame photometry) and creatinine[10]

Active and dummy tablets of chlorthalidone (50 mg) and capsules of triamterene (50 mg) were made available. For the first 3 weeks of the trial each patient received one dummy tablet of chlorthalidone daily and three dummy capsules of triamterene. This was known to the observers but not to the patients. Thereafter each patient received treatment for 6 weeks with each of the four possible combinations both dummy both active, active chlorthalidone and dummy triamterene dummy chlorthalidone and active triamterene. The order of administration was randomized and unknown to patient or observer although the patients were told that they would receive inert medication from time to time. In order that the observers should not be biased by knowledge of the results of estimations of plasma potassium or urea these results were not made known until the end of the trial The control level of blood pressure is the mean for the 6 weeks during which the patient was taking dummy tablets. The change in blood pressure is the difference between the control level and the mean of readings for 6 weeks while the patient received the active agents.

Results

I Effects on arterial pressure The effect on the blood pressure of the patients habituation to the examination was first tested by comparing the average blood pressure for all 11 patients in the first second third and fourth periods of treatment regardless of which drugs were given Since the order of administration of drugs was randomized there should be no significant difference between the levels of blood pressure in consecutive periods if no significant habituation took place. This was found to be the case there was no significant difference between consecutive periods (variance ratio 0 15 $p > 0.2$) and thus it was reasonable to assume that the changes observed were due to the action of the drugs given

The changes in blood pressure resulting from each regimen are summarized in Table II and Fig 1 It is apparent that triamterene alone, in a dose of 150 mg

Table II Mean changes in blood pressure plasma potassium uric acid urea and creatinine during each treatment

	Triamterene	*Chlorthalidone*	*Both*
Blood pressure (mm Hg) Mean fall ± 1 S.E.M Lying	7 2 ± 2 7/3 4 ± 2 3	15 7 ± 4 3/7 1 ± 2 4	19 3 ± 4 0/6 9 ± 2 1
Standing	3 6 ± 3 4/2 7 ± 1 8	18 4 ± 4 1/8 4 ± 2 2	23 8 ± 3 8/8 9 ± 2 2
Plasma potassium (mEq./L.) Mean change ± 1 S.E.M	+0 49 ± 0 13	−0 69 ± 0 08	−0 26 ± 0 12
Serum uric acid (mg /100 ml.) Mean change (on 9 patients only) ± 1 S.E.M	+0 82 ± 0 32	+1 29 ± 0 23	+1 36 ± 0 26
Plasma urea ratio Per cent control ± 1 S.E.M	91 4 ± 3 6	87 3 ± 4 6	74 9 ± 4 1
Plasma creatinine ratio Per cent of control ± 1 S.E.M	95 0 ± 3 3	91 9 ± 4 7	78 7 ± 4 5

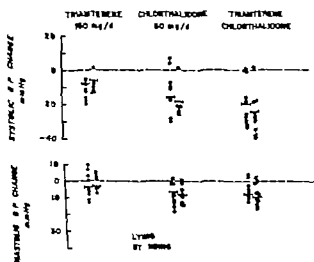


Fig 1 See text.

daily has very little effect on arterial pressure There was a mean fall of 7 2 mm Hg S E. ± 2.7 in systolic pressure measured with the patients supine. The fall of 3 4 mm Hg S. E. ± 2.3 in diastolic pressure did not differ significantly from zero Chlorthalidone in a dose of 50 mg daily caused a mean fall of 15 7 mm Hg S E. ± 4.3 in systolic pressure and of 7 1 mm. Hg S E. ± 2 4 in diastolic pressure Combination of the two drugs caused a slightly greater fall of 19.3 mm Hg S E. ± 4 0 in systolic pressure although this change is not significantly greater than that caused by chlorthalidone alone. The effect of the combination on diastolic pressure was *slightly but not significantly less than that* of chlorthalidone alone—a fall of 6 9 mm Hg S E. ± 2 1 Within the present group of patients unlike in those previously reported on there was no correlation between the control levels of blood pressure and the fall in arterial pressure induced by chlorthalidone. There was, however a significant relationship between the change in diastolic blood pressure caused by chlorthalidone in individual patients and that caused by triamterene (variance ratio 17 2 $p < 0 01$) as shown in Fig 2 There was no evidence that either drug caused a greater fall in blood pressure in the erect than in the recumbent position

2 Effect on renal function Concentrations of plasma urea and creatine were measured on three occasions in each 6-week period For each patient the changes are expressed as the

$$\frac{\text{average of 3 measurements during the control period}}{\text{average of 3 measurements during the period on any drug}} \times 100,$$

and for convenience are termed the *plasma urea ratio* and the *plasma creatinine ratio* Thus, no change in plasma level would be recorded as a ratio of 100 and an increase in plasma levels of urea or creatinine during administration of an active drug would give a ratio below 100 This method of expressing the data has been used because the ratio of plasma levels would provide

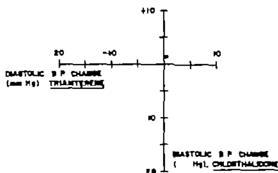


Fig 2 See text

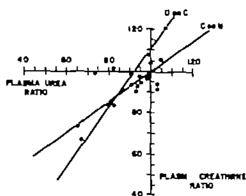


Fig 3 See text

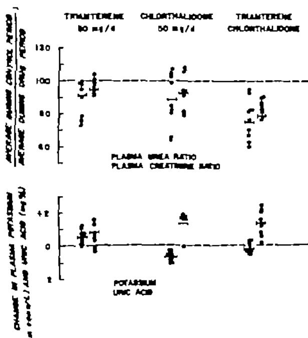


Fig 4 See text.

an estimate of change in urea or creatinine clearance if it be assumed that the daily excretion of urea and creatinine did not change significantly from one period to another Actual measurement of urea or creatinine clearance proved to be impossible because of uncertainty about the accuracy of 24-hour collections of urine on outpatients.[11] As shown in Fig 3 good correlation was observed between change in plasma urea ratio and change in plasma creatinine ratio (variance ratio 34 06, $p < 0.001$) although there is considerable scatter Thus, it seems to be likely that these methods are, in fact, estimating changes in clearances, although probably not very accurately

The changes in plasma urea and plasma creatinine ratios are shown in Table II and in Fig 4 All three treatment regimens caused a reduction in urea and creatinine ratios, indicating a rise in plasma urea or creatinine concentration and suggesting a fall in glomerular filtration rate. The decrease was greatest when the combination of drugs was given and least with triamterene both for plasma urea and creatinine ratios although the average ratios were slightly higher for creatinine than for urea with each treatment It seems to be likely that, on the average there is a small reduction in glomerular filtration during treatment with triamterene or chlorthalidone. In individual patients the reduction approached 50 per cent of the control ratio For any given treatment there was no relationship between the fall in blood pressure and the plasma urea or creatinine ratio

The concentration of plasma potassium rose when triamterene was given by an average of 0 49 S.E. ± 0 13 mEq per liter Chlorthalidone caused an average fall in potassium of 0 69 S E. ± 0 08 mEq per liter and the combined treatment caused a small and insignificant decrease of 0 26 S.E. ± 0 12 mEq per liter Both triamterene and chorthalidone caused an increase in serum uric acid which averaged 0 82 S.E. ± 0 32 mg /100 ml and 1 29 S E. ± 0 23 mg./100 ml respectively The combination caused an average rise of 1.36 S E. ± 0 26 mg /100 ml

Changes in weight were small and insignificant with all three treatments.

Discussion

Chlorthalidone in a relatively small dose causes a fairly consistent fall in arterial pressure of the same order as that found in previous investigations of similar design.[3,11] Triamterene, even in a fairly large dose has a very small effect upon elevated arterial pressure. This is similar to the observations of Rathsach and Hilden[12] who stated that triamterene had a much smaller effect upon elevated arterial pressure than did thiazide diuretics. We have found a significant correlation between the change in arterial pressure induced by chlorthalidone and that accompanying the administration of triamterene this suggests that both agents may affect blood pressure through the same mechanism. However it may be that this correlation is a function of the patient rather than the drug, i.e. that some patients will tend to have large and some small falls in blood pressure, regardless of which drug they take. This possibility can be investigated only by comparing patients' blood pressure responses to drugs that are known to act in different ways.

Both chlorthalidone and triamterene cause elevation of plasma urea and creatinine the proportional changes being similar. The drugs probably cause a sustained but reversible reduction in glomerular filtration which is not correlated with the changes in weight or in blood pressure. Combining the two drugs causes a further decrease in renal function without significantly affecting any of the other measured variables, except the level of plasma potassium. Since the concentration of plasma potassium rose during the administration of triamterene and fell with chlorthalidone it is very unlikely that the depletion of potassium is a significant influence in the retention of urea. This investigation sheds no further light on the mechanism responsible for the effect of diuretic agents on concentrations of blood urea and creatine.

It is clear that triamterene given alone in a dose of 150 mg daily has very little useful effect upon high blood pressure. Given in combination with chlorthalidone it will reduce the fall in plasma potassium caused by the latter this is similar to the findings of Heath and Freis[13] with respect to hydrochlorothiazide. There is little evidence to indicate that hypokalemia induced by diuretics is harmful except in patients receiving digitalis preparations. Triamterene prevents the hypokalemia at the expense of a further decrease in renal function and it seems to be unlikely that it is of much value in the treatment of essential hypertension. Although triamterene may prove to have a more marked hypotensive effect in patients whose hypertension is accompanied by marked retention of fluid and particularly in patients with pre-eclamptic toxemia the results of this investigation cannot be applied to such situations. Triamterene in the dose used here caused a rise in serum uric acid although this effect was not so marked as that of chlorthalidone when both drugs were given together the serum uric acid was not significantly greater than when chlorthalidone was given alone. Heath and Freis[13] did not find any significant difference between the levels of uric acid in patients given hydrochlorothiazide and the levels in patients given triamterene. This probably means that triamterene also caused an elevation of the levels of uric acid in their patients, but this is uncertain since no measurements were recorded while the patients were not receiving an active drug.

Summary

1. Eleven patients with moderately severe arterial hypertension were given chlorthalidone (50 mg daily) triamterene (150 mg daily) and placebo in a double blind crossover trial each *treatment* was given for 6 weeks, and blood pressure was measured at weekly intervals.

2. Triamterene alone had very little effect upon elevated arterial pressure whereas chlorthalidone caused a moderate reduction *in* systolic and diastolic pressures. A combination of the two drugs did not significantly increase the fall in arterial pressure.

3. Triamterene prevented the fall in serum potassium caused by chlorthalidone both drugs caused a rise in plasma creatinine and urea and in serum uric acid.

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The physiologic fallacy of adjusting for body weight in performance of the Master two-step test

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Master's "two-step" test is widely employed to give a standardized physiologic stress for the purpose of eliciting electrocardiographic changes in patients with coronary insufficiency. The test prescribes either a given number of trips up and down a set of two 9-inch steps in 90 seconds (single Master's test) or double the number of trips in 180 seconds (double Master's test). The number of trips is determined for each subject according to age and weight.

Ford and Hellerstein[1] and, later, Hellerstein and colleagues[2] claimed that the test has a sound physiologic basis, since the mean oxygen demand in their sample of 85 normal men and 71 cardiac patients was found to be 6.8 times the resting oxygen consumption regardless of age, weight, or state of health of the subject. The authors[2] found the double Master test to require on the average 1.485 ± 0.244 L. of oxygen per minute; however, there was a large variability. Assuming a symmetrical distribution, the 95 per cent normal limits of oxygen consumption ranged from about 1 to 2 liters.

The gradations in work rate established by Master and Oppenheimer[3] were designed to provide a physiologically equivalent work load for all individuals according to sex, age, weight, and height. Later, Master[4] established standards which excluded height.

From general physiologic principles it is doubtful whether in locomotion equality of external performance, in terms of the product of body weight and vertical distance moved, provides equality of physiologic load. Unfortunately, cardiac load in terms of myocardial oxygen consumption per gram of heart weight cannot be determined readily during exercise. Simonson[5] pointed out that total oxygen consumption per kilogram of body weight during submaximal exercise *must* provide a good approximation because of the high correlation between body weight and heart weight. Since Master's test is the most commonly used test in the diagnosis of suspected coronary insufficiency, the hypothesis involved has

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been tested experimentally and the physiologic basis of the standardization has been evaluated further

Subjects

A total of 14 normal male subjects ranging in age from 12 to 27 years was studied Body weights of the subjects ranged from 39 4 to 97 3 kilograms. All had normal resting and postexercise electrocardiograms and blood pressures.

Methods

Prior to the actual experiment all subjects performed at least once (or until done correctly) the step test as prescribed by Master for a specific age and body weight. In addition the procedure was repeated at a constant rate of 40 steps per 180 seconds. For the experiment subjects were post absorptive. After the subject had been ated at rest for 20 minutes, a standard 2-lead ECG was recorded followed by de rmination of resting (subject still seated) ygen consumption Then the subject per rmed the double Master two-step test xpired air was collected throughout the 30-second test in a 180-liter balanced spirometer through a low resistance valve and tubing supported above the subject's head Immediately at the cessation of the test the subject was seated and a standard 12 lead ECG was taken while expired air was diverted to a second balanced spirometer and collected for 10 minutes. After heart rate returned to the pre-exercise resting level the test was performed at the fixed rate of 40 steps per 3 minutes. Samples of gas were analyzed for CO_2 and O_2 by the Haldane technique. Tests were repeated in 12 of these subjects under the same experimental conditions. No oxygen debts were obtained from 2 subjects during the first experiment Total net oxygen consumption was defined as the oxygen intake for 3 minutes of work plus oxygen debt, which was derived from the oxygen consumption for 10 minutes of postexercise recovery less the resting oxygen consumption for a corresponding period of time.

Results

Grouped data including individual ages and body weights, are summarized in Table I Means standard deviations (S.D) and coefficients of variation (i e. S D as per

able I Age and body weight of 14 normal subjects and their gross net oxygen consumption vork plus debt less resting oxygen consumption) during the double Master two-step test and ie same step test at a constant rate of 40 steps per 3 minutes

Subject	Age (yr)	Weight (Kg)		Master's test (liters O_2/3 min.)		40-Step test (liters O_2/3 min)		Master's test (ml. O_2/Kg /3 min)		40-Step test (ml O_2/Kg /3 min.)	
		1	2*	1	2	1	2	1	2	1	2
W.A.	20	70 6	71 2	3 396†	5 383	3 279†	4 469	48 1†	75 6	46 5†	62 7
B.A.	24	96 6	97 3	5 850	5 573	6 728	5 923	60 5	57 3	69 6	60 9
D B	23	78 5	78 4	6 132	6 008	5 658	5 240	78 1	76 6	72 1	66 8
C.B	19	69 1	69 2	5 502	5 342	5 466	4 393	79 6	77 2	79 1	63 5
A.F	14	40 7	—	3 954	—	2 596	—	97 1	—	63 8	—
W.N	19	64 9	64 7	4 315	4 789	4 000	4 402	66 5	74 1	61 6	68 1
F.P	25	96 4	96 4	6 185	5 835	6 130	5 752	64 1	60 5	63 6	59 6
R.R.	26	89 4	89 4	6 737	6 474	5 597	5 755	75 4	72 4	62 6	64 4
D T	14	42 2	39 4	3 780	3 755	3 125	2 803	89 6	95 4	4 1	71 2
G.T	19	68 2	67 8	3 096†	4 550	2 841†	4 018	45 4†	67 1	41 7†	59 2
J.F	27	68 7	68 4	5 541	5 438	4 541	4 220	80 6	79 5	66 1	61 7
R.S.	23	93 5	—	6 362	—	7 061	—	68 1	—	75 5	—
J T	14	42 6	42 6	4 933	4 230	3 112	3 004	115 7	99 2	73 0	70 5
E.S.	12	42 2	42 2	3 906	4 098	2 800	2 306	92 6	97 1	66 4	54 6

*Indicates first and second determinations (different days)

†No determinations of oxygen debt.

*Table II. Net oxygen consumption (gross and per kilogram of body weight) for 3 minutes of two-step exercise according to the procedure of Master and at a constant rate of 40 steps per 3 minutes—mean values with standard deviations (S.D.) and coefficient of variability (S.D. per cent of mean) for 10 normal subjects**

Oxygen consumption	S.D.	S.D. per cent of mean
5.22 L.†	1.34	25.6
4.55 L.‡	1.90	41.7
79.6 ml./kg.†	21	26.7
66.5 ml./kg.‡	6.3	9.4

*Four subjects were omitted—2 lacked one oxygen-debt measurement, and 2 were not retested.
†Procedure: Master test.
‡Procedure: Forty step test.

cent of the mean) are given in Table II for net oxygen consumption for exercise, which is expressed both as liters and as milliliters per kilogram of body weight, each for 3 minutes. The variation in total net oxygen consumption is less for the Master test than for the 40-step test when values are expressed absolutely (liters per 3 minutes). When values are expressed per unit of body weight, however, the coefficient of variation of the 40-step test (9.4 per cent) is much less than that of the Master test (26.7 per cent). Therefore, correction of oxygen consumption for body weight reveals that the S.D. of the energy expenditure is substantially less when the rate of work is held constant.

Despite the relatively greater severity of work imposed upon lighter subjects by Master's two-step test, as shown by greater oxygen requirements per kilogram of body weight for these men (Table I), there were no significant changes in ECG other than increased heart rate. Return of heart rate to resting level was, however, considerably slower in the lighter subjects than specified by Master[3] for a normal response. This clearly reflected greater physiologic stress for these individuals.

Discussion

After age 12 to 13 years there is either very little or no decrease in mechanical efficiency[8] in response to a fixed task, up to about 70 years. Since our subjects were chosen within an age range in which mechanical efficiency is constant, our arguments are broadly applicable. Master's corrections for body weight introduce major changes in physiologic cost, whereas known age trends in mechanical efficiency result in only very minor changes in cost.

The real question is whether a test which requires approximately the same total energy expenditure for all individuals of the same sex provides a physiologically equivalent work load. It is clear from Table II that expression of the oxygen consumption per kilogram of body weight has the effect of increasing slightly the interindividual variability of the Master two-step test while decreasing that of the 40-step test. The fallacy of equating physical work (foot pounds) and physiologic load has been briefly discussed by Simonson and Keys[14] and more recently by Simonson.[8] Åstrand and co-workers[1] found close correlations between body weight and the following: blood volume, heart size, maximum cardiac output, and maximal oxygen intake. From his observations on the relationship of body size to metabolic rate, Kleiber[13] concludes that the influence of body size on metabolism is related to oxygen transport. Calculations from data summarized by Kleiber[13] show a nearly constant oxygen transport per kilogram of body weight per heart beat over a wide range of body weights among mammals (horse to mouse). Evaluation of work output in terms of the degree of stress upon the cardiovascular system must therefore be related to the proportional stress upon this system. This is most readily accomplished, although not perfectly, by expressing oxygen uptake per unit of body weight. Differences in body composition (e.g., obesity) and the degree of physical conditioning also modify this relationship.

In evaluating the severity of exertion of Master's test, Ford and Hellerstein[2] conclude that it constitutes moderately severe exercise, demanding 45 per cent of the mean maximal oxygen intake observed in young men by Taylor and co-workers.[12] Indeed, Taylor and colleagues have shown that the maximal oxygen intake is a highly reproducible and sensitive index of maximal cardiovascular performance. How then is

maximal oxygen intake related to age and body weight

Robinson[8] found in males a progressive decrease in maximal oxygen intake with advancing age over 20 years. This means that any fixed metabolic rate for exercise constitutes a greater fraction of the maximal oxygen intake as age increases, and thereby represents a greater physiologic load. Robinson found for example at mean ages of 6 1 10 4 17 4 and 63 1 years mean maximal oxygen intakes of 0 98 1 56 3 61 and ? 35 L per minute respectively. It is clear that a test requiring an identical rate of oxygen consumption requires markedly different percentages of the maximal oxygen intake at different ages. For example the double Master test was found by Ford and Hellerstein[3] to require 1 485 ± 0 244 L. of oxygen per minute, and by us 1 740 ± 0 445 L. O_2 min. The latter figure constitutes respectively 176 112 48 and 74 per cent of the maximal oxygen intakes of the four groups from Robinson's data and is clearly not a physiologically equivalent stress. Åstrand's[7] figures show a similar trend with age up to 20 to 33 years the oldest group studied by him. Although on the average maximal oxygen intake values in Åstrand's group were higher the same conclusion is reached when the cost of the double Master test is expressed as a per cent of these values.

Ford and Hellerstein[3] also expressed their findings for the energy requirement of the double Master test as a multiple of resting oxygen consumption the average value being 6 8 times the metabolic rate at rest. Åstrand[7] found the maximal oxygen intake of boys 7 to 9 years old and of male adults 20 to 33 years old to represent 9 4 and 15 ı times their respective basal values. Thus by this criterion of Ford and Hellerstein also the requirement of the double Master test is not physiologically equivalent.

Considering maximal oxygen intake per kilogram of body weight clarifies further the physiologic meaning of the problem. Both Robinson[8] and Åstrand[7] found relatively small differences in maximal oxygen intake per kilogram of body weight between the ages of 7 years and 20 to 30 years. The former investigator found the age range of mean values to be from 46 7 ml of oxygen per kilogram per minute at mean age 6 1 to 43 1 ml O_2 Kg/min at mean age 35 1 with a ceiling average of 52.8 at age 17 4 years. Åstrand[7] observed higher mean values for all age groups studied and little or no age trend namely 56 9 and 58 6 ml O_2/Kg/min at respective ages of 7 to 9 years and 20 to 33 years, a difference of only 3 per cent. In contrast the oxygen requirement per kilogram of body weight of the double Master test was found in this study to range from 19 1 to 38 6 ml per minute over the same age range, a difference of 102 per cent.

Ideally to provide a physiologically equivalent metabolic load a test would require the same fraction of the maximal oxygen intake. This would of course, also tend to make the oxygen debts incurred by the task less varied among different individuals. However determination of the maximal oxygen intake is time consuming and difficult to make in patients. Therefore a test which requires of all individuals of the same sex the same oxygen consumption per kilogram is indeed desirable. There is the additional reason that, at a given oxygen intake per kilogram of body weight, cardiac output per unit of body mass is quite constant[14] thus producing a constant load upon the heart in respect to its relative mass.

The increased availability of the motor driven treadmill to hospitals and clinics offers an easy solution to this problem. Unlike the bicycle ergometer work (at the same speed and grade) on a treadmill requires an oxygen consumption per kilogram of body weight which is remarkably constant among different individuals.[13] Unlike the step-test or bicycle ergometer there are only minimal differences due to skill or training between determinations in the same individual. Erickson and associates[15] observed that expression of oxygen requirement per unit of body weight decreased the coefficient of variability between individuals from 9 37 per cent—when gross oxygen consumption was used—to 3 99 per cent. The coefficient of variability between trials in the same individuals was only 2.68 per cent, and 2.50 per cent when data were expressed both in terms of gross oxygen consumption and per unit of body weight respectively.

Exercise tests requiring the same oxygen consumption per kilogram of body weight have been successfully devised through use of the treadmill by Simonson and Keys[10] and by Bruce and colleagues.[16] Indeed the latter investigators found that the most effective means of differentiating cardiac patients from normal subjects has been an estimate of total oxygen consumption per kilogram of body weight.

The conclusion is that the variable number of steps employed in the Master two-step test does not result in physiologically equivalent loads. Indeed the lighter subjects are more heavily taxed by this procedure. Only when such a test is carried out at a constant rate does oxygen cost per kilogram of body weight approach a nearly constant value, thereby providing a physiologically more equivalent stress on the circulatory system.

Summary

The physiologic load imposed by the double Master two-step test and by a similar step test in which work was carried out at a rate of 40 steps per 3 minutes was evaluated in 14 male subjects having a wide range of body weights. Gross oxygen consumption varied less among individuals during the Master procedure (the S.D. was 25.6 per cent of the mean) than during the 40-step test, in which all subjects worked at the same rate (the S.D. was 41.7 per cent of the mean). However expression of energy requirements per unit of body weight decreased the coefficient of variation for the energy cost of the 40-step test (9.4 per cent) well below that of the Master test (26.7 per cent). Oxygen requirements per kilogram of body weight were very high for lighter subjects reaching 38.6 ml. per minute and very much less for heavy subjects (minimum, 19.1 ml. per minute). The lightest subjects were therefore, approaching their maximal oxygen intakes while the heavier men were farthest from maximal. These data illustrate the error in decreasing the rate of work for heavier subjects performing the step test, and demonstrate that the Master procedure fails to provide a physiologically equivalent work load for individuals differing in body weight.

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The acute and chronic effects of phlebotomy on general hemodynamics and pulmonary functions of patients with secondary polycythemia associated with pulmonary emphysema

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The utilization of phlebotomy in the therapeutic management of patients with polycythemia secondary to pulmonary disease is still controversial. Striking improvements have been stated to occur after the procedure.[1] On the other hand, although improvements in the hemodynamic status have been noted immediately after venesection, it is not known whether such improvements are sustained.[2] It appeared to be possible that polycythemia resulting from chronic arterial hypoxemia might be a compensatory homeostatic mechanism which, if carried to extreme levels, might in itself lead to serious difficulties and impose an additional load on the already overburdened systemic and pulmonary circulations. The following studies were made in order to evaluate this premise and to determine whether phlebotomy would be advantageous or harmful in the management of patients having chronic pulmonary emphysema with polycythemia.

Material and methods

Fifteen patients with chronic pulmonary emphysema and hematocrit levels of 50 per cent or greater were selected for the study. Pulmonary function studies were performed 1 day prior to and on the day after right heart catheterization and included the following: (a) The vital capacity and timed vital capacity[4] were measured by a 13.5 liter Collins respirometer with the patient in the sitting position, the volumes being corrected to body temperature saturated with water vapor at ambient pressure (B.T.P.S.), and the predicted vital capacity volumes obtained from a nomogram based on height and age for men over 40.[4] (b) Studies were made of recumbent static lung volumes by open-circuit nitrogen rinse out with 7 minutes of oxygen breathing[5] monitored by a Waters nitrogen meter. Lung volumes were corrected to B.T.P.S. and predicted lung volumes[6] were based on height, age, and sex. (c) The maximum breathing capacity was measured by an open-circuit technique, with expired gas collected in a Douglas bag for 20 seconds using a Rudolph valve and large-bore tubing. The volume was measured in a Tissot spirometer and expressed as liters per minute at body temperature and the

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predicted maximum breathing capacity calculated according to Wright's formula.[7] (d) The breathing response to a standard exercise was measured by collecting expired air during the fifth and sixth minutes of walking at the rate of 2 miles per hour on the level the volume being expressed in liters ventilated B T P.S. per square meter of body surface area per minute.[8]

At cardiac catheterization pressures were recorded sequentially from the right atrium and ventricle and in the wedged pulmonary position Pressures from the brachial and pulmonary arteries and the electrocardiogram were inscribed simultaneously on a suitable direct writing oscillograph. Mean pressures were derived by planimetric integration of the pressure curves. Tabulated central venous and peripheral arterial pressures were the averages of two recordings prior to and three after the determination of the cardiac output.

All specimens of blood were withdrawn in duplicate and oxygen contents were determined spectrophotometrically Whole blood viscosity compared with water was determined using the Ostwald viscosimeter.[10] Expired air measured through a dry gas test meter was collected in Douglas bags (4 minutes) and the oxygen content obtained by passage through a Pauling oxygen analyzer All volumes were corrected to S T P The maximal acceptable difference between two successive oxygen consumption and cardiac output check determinations was 10 per cent. Right and left ventricular work, pulmonary vascular resistance, and total pulmonary and peripheral resistances were calculated by conventional formulae Samples of arterial blood for oxygen and carbon-dioxide tensions were withdrawn immediately prior to the determination of the cardiac outputs. Arterial oxygen and carbon-dioxide tensions were determined at body temperature by the direct bubble equilibration technique.[11]

After the basal determinations, 300 to 1 000 ml of blood were withdrawn rapidly via the indwelling arterial needle. The amount removed was dependent upon the original hematocrit level Three hundred milliliters were removed when the hematocrit was between 50 and 55 per cent, and 1 000 ml when the level was 65 per cent or greater The patient was allowed to rest for 1 hour and the catheterization studies were repeated Subsequently the patient was followed in the outpatient clinic where sufficient blood was withdrawn at frequent intervals to decrease and maintain the hematocrit between 45 and 50 per cent No other change in therapy was instituted The patients were re-evaluated at an interval of 5 to 6 weeks by repeat cardiac catheterization and pulmonary function studies

Results

1 One hour post phlebotomy The measured and calculated hemodynamic data appear in Tables I and II and pulmonary function data in Table III Significant ($p =$ or less than 0 01) decreases occurred in the hematocrit level and in right atrial and right ventricular end-diastolic pressures Significant increases were observed in arterial oxygen saturation and tension, and there were alterations of probable significance ($p < .05 > .01$) in the oxygen consumption, which was increased and right ventricular systolic and mean pressures, which were decreased There were no significant changes in arterial CO_2 tension, viscosity cardiac index, pulmonary capillary pressure, pulmonary arterial pressure brachial arterial pressure, total pulmonary and peripheral resistances, pulmonary vascular resistance and right and left ventricular work.

Pulmonary function studies on the following day for the whole group showed no significant alterations in any of the parameters as compared with the pre-phlebotomy data. However evaluation of the data from patients with high end-diastolic pressures in the right ventricle (Table IV) revealed significant decreases in residual volume and functional residual capacity

2 Follow up Significant decreases occurred in the hematocrit level, viscosity oxygen-carrying capacity arterial oxygen content and the oxygen content of mixed venous blood There was also a decrease of probable significance in the walking ventilation. All other measurements and calculations related to the pulmonary function and hemodynamic status of the patients showed no change from the control pre-phlebotomy data

Discussion

Alterations in pulmonary function have been noted to follow venesection. Ca

Table 1 Blood gas and hemodynamic data

Patient	Procedure	Hct (%)	Viscosity	O sat (%)	PO (mm Hg)	PCO$_2$ (mm Hg)	O cons (ml./min.)	A V O$_2$ (vol %)
1	A	63		67	27	61	194	4 4
C B	B	59		75	37	52	184	4 4
	C	49		58	38	55	79	4 2
2	A	56	5 93	78	39	42	166	4 2
F H	B	54	5 91	80	44	42	164	4 8
	C	47	4 15	80	44	43	130	4 1
3	A	56		80	40	50	114	4 1
R R	B	53		83	47	33	115	5 4
	C	43		60	34	41	190	3 9
4	A	56		80	39	48	132	3 9
F K	B	54		85	45	39	177	4 9
	C	44		90	68	35	292	4 1
5	A	53		74	46	36	199	5 1
C I	B	52		79	49	34	157	5 7
	C	43		79	48	44	154	4 5
6	A	59	7 04	76	40	45	208	7 1
A B	B	55	7 35	80	44	43	220	7 7
	C	42	4 26	65	43	50	176	5 4
7	A	66	7 40	40	24	53	134	5 2
H I	B	61	5 70	45	30	45	155	5 6
	C							
8	A	53	5 06	86			258	5 2
F I	B	53	5 12	89			347	6 0
	C	42	3 70	87			188	4 3
9	A	50	4 10	71	37	57	141	4 5
M C	B	49	3 90	77	42	45	170	4 8
	C							
10	A	57	5 64	57			170	5 0
I M	B	56	5 52	60			163	4 7
	C	44	3 82	61			111	3 5
11	A	59	6 30	64			231	3 9
F T	B	58	5 90	62			277	4 2
	C	41		68			219	4 1
12	A	51	6 10	94	77	34	178	4 9
M D	B	49	4 60	95	78	39	160	5 5
	C	50	6 70	94	80	37	198	6 1
13	A	53	5 80	81	62	42	230	4 2
R K	B	52	6 20	89	62	41	309	5 0
	C	43		88	75	45	213	4 7
14	A	53		92	89	29	170	7 3
J P	B	53		91	97	31	200	7 7
	C	49						
15	A	59		85	59	40	191	4 4
S.K.	B	58		87	68	34	240	5 1
	C							
Averages	A	56 3	5 93	75	48 2	44 7	181	4 9
	B	54 4	5 57	78	53 5	41 3	198	5 4
	C	44 2	4 52	75	53 0	45 0	177	4 5
p Value	B	<0 001	>0 1	<0 001	<0 001	>0 05	>0 025 <0 05	<0 001
	C	<0 001	0 01	0 5	>0 1	>0 3	>0 3	>0 2

A Control. B One hour post-phlebotomy. C Follow up at 5 to 6 weeks. Hct: Venous blood hematocrit. O$_2$ sat. Oxyhemoglobin [illegible] oxygen difference. C.I.: Cardiac Index. R.A. Right atrial pressure. R.V.: Right ventricular pressure. P.A. Pulmonary arterial pressure.

C.I (L/M/min.)	R.A mean (mm Hg)	R.V (mm Hg)	R.V (mean)	P.A (mm Hg)	P.A (mean)	P.C. (mm Hg)	B.A (mm Hg)	B.A (mean)
3 0	−0 1	39/3	15 2	45/26	34	2 1	96/68	75
2 8	−1 2	32/1	9 8	34/22	26		95/65	75
1 2	2 1	41/3	17 0	50/28	35	7 2	107/75	85
2 3	3 7	76/3	23 0	62/27	37	9 8	126/67	87
2 1		50/4	17 4	60/25	34	5 3	110/63	77
1 8	2 5	46/4	16 5	51/19	29	7 3	101/55	73
1 7	0 9	40/10	19 2	45/15	24	6	92/58	66
1 3	1 0	28/−1	9 2	36/13	17	0 3	94/58	66
3 0	3 0	51/5	12 0	63/23	34	6 2	93/49	69
1 9	0 7	38/3	7 9	30/10	17	14 3	128/60	84
2 0	2 6	30/4	7 3	28/13	17	5 0	125/64	81
3 9	4 1	38/6	11 5	38/10	21	10 5	154/72	100
	2 9	41/4	16 4	42/24	31	4 1	92/61	69
	1 3	34/1	10 0	36/20	27	6 0	91/66	72
	1 3	28/2	11 2	37/20	27	6 4	94/37	69
1 9	4 0	65/4	12 0	86/16	46		154/81	94
1 9		70/3	6 5	74/80	39		128/67	88
2 1	6 7	70/10	28 4	76/31	48	12 4	120/60	82
1 9	10 9	59/16	27 6	56/35	41	7 0	100/74	79
2 1	3 9	65/9	22 2	63/39	46	6 9	88/64	74
2 2	4 0	39/8	16 8	32/19	25	11 6	140/88	110
2 5	4 1	36/9	20 0	36/20	26	14 6	138/87	110
1 9	8 8	38/9	21 0	36/20	27	9 1	126/78	98
1 9	2 4	43/4	13 5	34/21	32	5 0	93/52	68
2 2	0 7			62/24	37	8 8	97/54	69
2 0	5 1	63/9	23 6	70/33	47	4 0	112/75	88
2 0	2 1	62/5	23 4	67/32	45	1 9	127/82	100
1 8	10 5	64/14	31 0	61/36	45	8 7	103/65	78
3 9	4 9	56/14	27 7	46/27	35	9 8	116/60	82
4 3	3 2	41/6	20 8	43/26	32	7 3	88/47	62
3 6	2 1	30/5	11 5	30/14	23	6 8	118/53	70
2 0	7 9	31/12	19 0	21/13	18	16 5	158/80	106
1 6	7 9	31/10	15 1	23/12	17	10 6	140/67	96
1 9	15 7	32/7	22 8	27/17	21	18 3	160/88	125
2 5	4 0	36/5	12 9	33/21	27	9 3	109/73	87
2 8	2 7	36/3	15 4	36/22	29	16 2	123/79	93
2 1	8 1	38/10	19 6	37/19	28	14 4	101/66	81
1 5	4 2			55/31	39	12 3	123/66	85
1 6	−0 2	51/3	17 4	44/26	34	4 6	103/61	77
	2 7	35/3	12 0	45/21	27	6 8	120/60	80
2 6	2 8	33/3	11 9	38/16	26	3 9	120/71	85
2 8	−0 9	25/0	10 3	32/13	22	1 8	110/63	81
2 25	4 1	47/7 1	17 7	47/22	31 8	8 0	117/69	84 3
2 28	2 1	43/4 1	14 0	45/21	29 8	6 9	111/66	81 4
2 31	6 4	43/6 8	18 4	46/22	30 6	9 6	116/65	84 5
>0 5	<0 01	>0 02 <0 03	>0 01	>0 5	>0 05	>0 2	>0 05	>0 1
		<0 01	<0 025	>0 2			>0 1	
		>0 2		>0 5			>0 4	
>0 3	<0 05	>0 5	>0 5	>0 5	>0 1	>0 2	>0 8	>0 1

mm. PO_2 Partial pressure oxygen. PCO_2 Partial pressure carbon dioxide. O_2 cont Oxygen content [illegible] A. Ox Arteriovenous ox [illegible]
P.C Wedge pressure. B.A Brachial arterial pressure

Table II Calculated indices from hemodynamic measurements

Patient	Experiment*	Total pulmonary resistance (dynes sec cm⁻⁵)	Pulmonary vascular resistance (dynes sec. cm⁻⁵)	Right ventricular work (Kg./min./M²)	Total peripheral resistance (dynes sec cm⁻⁵)	Left ventricular work (Kg./min./M²)
1	A	606	569	1 39	1 338	3 07
C.B	B	502		0 98	1 441	2 83
	C	1 484	1 181	0 59	3 557	1 42
2	A	723	530	1 23	1 708	2 90
F.H	B	788	665	0 71	1 797	2 17
	C	771	573	0 69	1 984	1 78
3	A	676	602	0 55	1 884	1 50
R R	B	649	638	0 31	2 488	0 87
	C	560	438	1 38	1 132	2 79
4	A	394	59	0 43	1 981	2 14
F K.	B	368	258	0 46	1 765	2 20
	C	237	119	1 12	1 124	5 31
5	A	629	546		1 406	
C.P	B	779	605		2 091	
	C	644	494		1 610	
6.	A	1 257		1 17	2 554	2 39
A B	B	1 090		0 92	2 459	2 20
	C	1 150	850	1 37	1 985	2 36
7	A	1 261	1 046	1 06	2 421	2 04
H T	B	1 311	1 113	1 28	2 103	2 05
	C					
8.	A	399	213	0 73	1 804	3 20
E.L.	B	356	158	0 90	1 490	3 80
	C	487	320	0 69	1 793	2 53
9	A	838	709	0 84	1 759	1 77
M C.	B	825	627	1 10	1 545	2 08
	C					
10.	A	1 087	994	1 25	2 044	2 35
L M	B	1 041	997	1 01	2 288	2 68
	C	1 104	905	1 11	1 922	1 43
11	A	465	331	1 83	1 099	4 30
F T	B	352	291	1 83	703	2 64
	C	345	244	1 13	1 038	3 39
12.	A	389	287	0 48	2 330	2 85
M D	B	473	183	0 40	2 634	2 09
	C	521	71	0 53	3 072	3 12
13	A	394	251	0 90	1 263	2 93
R.K.	B	378	166	1 09	1 219	3 52
	C	485	233	0 78	1 413	2 27
14	A	1 356	978	0 77	2 935	1 67
J.P	B	1 045	903	0 76	2 371	1 70
	C					
15	A	484	412	0 90	1 561	2 91
S.K.	B	368	337	0 80	1 359	3 04
	C					
	A	730	538	0 97	1 872	2 57
Averages	B	688	534	0 90	1 850	2 42
	C	708	495	0 94	1 875	2 64
p Value	B	>0 1	>0 1	>0 1	>0 1	>0 1
	C	>0 1	>0 1	>0 1	>0 1	>0 1

*A Pre-phlebotomy B: One hour post phlebotomy C Follow up at 3 to 6 weeks

and McMichael[11] reported increases in total lung volumes and vital capacity in normal individuals after phlebotomy whereas more recently Auchincloss and Duggan[3] observed increases in functional residual capacity residual volume, and total lung capacity but no significant changes in vital capacity in patients with chronic pulmonary emphysema and secondary polycythemia The results of the present study differ from both of those reports, in that the pulmonary function studies were essentially unchanged for the over-all group after both acute and longer term venesections. Only in patients with evidence of right heart failure indicated by high end-diastolic right ventricular pressures did significant changes in pulmonary function occur These individuals showed significant decreases in residual lung volume and functional residual capacity The observed reductions in the right atrial and right ventricular end-diastolic pressures in the over-all group present 1 hour after phlebotomy as well as the changes in pulmonary function in the patients with right heart failure could be attributable to a possible reduction in the blood volume in the lungs, right heart and peripheral venous bed This explanation might appear to be unlikely since the hematocrit showed a significant decrease at the time the pressures in the right heart were remeasured which suggests that fluid readjustments had occurred in the direction that would have tended to restore the blood volume However the hypothesis cannot be excluded on the basis of the change in hematocrit alone since it is unlikely that the blood volume would have been restored in the short period of 1 hour

The long term effects of repeated phlebotomies and the maintenance of hematocrits at nearly normal levels are those which might be expected and predicted to result from the mechanical removal of red blood cells. Thus, the decreases in hematocrit, oxygen-carrying capacity and arterial and venous oxygen content can all be explained on this basis. Beyond these changes since no significant alterations occurred in either the hemodynamic or pulmonary function status of the patients, it must be concluded that long term phlebotomy is neither helpful nor harmful to these patients. The data confirm the observations reported by Hecht, Gaylor and Stein[14] relative to the hemodynamic status of such patients and extend the observations to indicate that no improvement in pulmonary function may be expected from the procedure.

There is a definite place for the utilization of phlebotomy in patients such as those observed in this study The first is the time honored employment of venesection to decrease viscosity in order to reduce the possible incidence of thromboembolic complications. For this purpose, repeat phlebotomies are indicated to produce decreases in the levels of hematocrit to the point at which viscosity will also be altered In the absence of viscosity measurements, since the data indicate that there are no obvious deleterious effects from long term phlebotomy the hematocrit may be reduced to normal levels. The second indication would be in relation to the acute status of the patient. Since significant decreases occurred in the right atrial and end-diastolic right ventricular pressures, it suggests that patients with cor pulmonale polycythemia, and right-sided failure would be benefited by venesection The observed increase in O_2 tension and saturation may also benefit a patient in heart failure In the acute studies a consistent observation was the increase in arterial oxygen tension and saturation A decrease in the venous-arterial shunting[11] and or a reduction in the pulmonary intracapillary blood volume with a reduced diffusing distance to the red blood cell, are hypothetical explanations for this effect. However the blood volume was not measured Alternatively alterations in the distribution of blood flow in the pulmonary vascular bed resulting from a possible decrease in the intrapulmonary volume could account for these changes. The acute changes in the residual volume and functional residual capacity in the patients with heart failure suggest that structural rearrangements may occur within the lung after the use of phlebotomy Although these changes in volume may not be statistically significant in patients not in failure enough rearrangement might occur to produce redistribution of blood flow leading to the observed improvement in O_2 saturation and tension The failure to observe similar changes in the residual lung volume functional residual capacity and oxygen saturation and tension after repeat phlebotomies indicates the possibility that with th

Table III Pulmonary function studies

Patient	Procedure	Vital capacity before bronchodilators: V.C. (liters)	Vital capacity before bronchodilators: F.E.V. (liters)	Vital capacity before bronchodilators: F.E.V. (liters)	Vital capacity after bronchodilators: V.C. (liters)	Vital capacity after bronchodilators: F.E.V.$_{1.0}$ (liters)	Vital capacity after bronchodilators: F.E.V.$_{3.0}$ (liters)
1 C.B	A	2 0	0 77	1 37	2 5	1 75	2 30
	B	2 2	0 81	1 10	2 6	1 24	2 00
	C	1 7	0 49	0 98	2 8	1 06	1 65
2 R.R.	A	2 0	0 73	1 06	3 1	1 28	1 83
	B	2 3	0 85	1 20	3 2	1 07	1 66
	C						
3 F.K.	A	1 9	1 41	1 71	2 0	1 62	1 82
	B	2 1	1 58	1 83	2 3	1 71	2 00
	C						
4 C.P	A	1 6	0 45	0 82	2 8	0 75	1 50
	B	2 9	0 60	1 17	3 5	0 97	1 47
	C	2 4	0 52	0 94	3 5	0 68	1 30
5 A.B	A	1 9	0 73	1 12	2 3	0 92	1 33
	B	1 8	0 62	0 89	2 2	0 88	1 35
	C	1 9	0 65	1 24	2 0	0 79	1 26
6. H.T	A	1 1	0 31	0 52	1 2	0 32	0 61
	B	1 2	0 26	0 45	1 5	0 31	0 58
	C						
7 E.L	A	3 1	1 60	2 24	4 1	2 13	2 83
	B	3 0	1 99	2 34	3 6	1 98	2 92
	C	3 3	1 43	2 18	4 2	2 09	3 08
8 M.C	A	3 0	0 76	1 30	3 6	0 92	1 82
	B	2 7	0 73	1 20	3 0	0 84	1 65
	C						
9 L.M	A	2 6	0 75	1 30	2 7	0 70	1 34
	B	2 8	0 65	1 21	3 1	0 74	1 32
	C	2 5	0 72	1 22	3 2	0 72	1 37
10. F.T	A	1 8	0 94	1 29	1 9	1 12	1 33
	B	1 9	0 89	1 37	1 8	0 96	1 37
	C	1 9	1 03	1 56	2 3	1 11	1 53
11 M.D	A	2 5	1 07	1 64	3 2	1 68	2 15
	B	2 9	1 37	1 92	3 7	1 83	2 47
	C	2 4	1 13	1 70	3 2	1 67	2 42
12. R.K.	A	3 1	1 18	1 97	3 6	1 31	2 24
	B	3 5	1 32	2 20	4 1	1 85	2 82
	C	4 1	1 44	2 45	4 6	1 69	2 69
13 S.K	A	2 1	0 67	1 38			
	B	2 7	0 72	1 67			
	C						
14 J.P	A	2 5	0 74	1 37	2 7	0 86	1 38
	B	2 2	0 57	1 28	2 3	0 70	1 28
	C	2 1	0 71	1 23	2 6	0 93	1 55
Averages	A	2 2	0 87	1 36	2 7	1 18	1 74
	B	2 4	0 93	1 42	2 8	1 16	1 76
	C	2 5	0 90	1 50	3 2	1 19	1 87
p Value	B	>0 1	>0 1	>0 1	>0 1	>0 1	>0 1
	C	<0 1	>0 1	>0 1	>0 1	>0 1	>0 1

A: Control. B: One hour post-phlebotomy C: Following at 5 to 6 weeks. V.C.: Vital capacity F.E.V.: Forced expiratory volume at Total lung capacity F.R.C.: Functional residual capacity E.R.V. Expiratory reserve volume. R.V. Residual volume. Terminal

MBC (L./min.)	W.V.—2 mph (L./min.)	T.L.C. (liters)	I.C. (liters)	Lung volume			Terminal alv. N (per cent)
				F.R.C. (liters)	E.R.V. (liters)	R.V. (liters)	
35	9 4	6 1	1 9	5 1	0 96	4 1	8 7
39	7 9	6 2	1 8	5 2	0 83	4 4	11
32	7 0	5 8	1 9	4 7	0 73	3 9	7 9
37	9 2	6 8	2 6	4 7	0 68	4 0	14 4
32	8 4	6 5	2 8	4 7	0 91	3 8	15 0
41	9 7	5 6	1 9	4 2	0 46	3 7	13 0
51	10 0	4 6	2 4	2 8	0 62	2 4	6 8
32		5 9	1 4	4 9	0 45	4 5	10 6
42		6 8	2 0	5 3	0 83	4 5	13 8
31		7 6	1 5	6 7	0 70	6 0	18 0
39	10	4 8	1 3	4 1	0 53	3 6	5 4
39	9 8	4 2	1 6	3 2	0 52	2 6	5 4
38	9 0	3 8	1 1	3 1	0 53	2 5	5 3
32		5 6	1 1	4 7	0 26	4 4	13 6
30		5 5	1 5	4 4	0 39	4 0	12 5
74	9 1	6 3	2 6	3 7	0 .8	3 5	2 2
78	8 5	6 4	2 8	3 4	0 26	3 2	2 2
83	8 3	6 6	2 7	3 8	0 36	3 4	4 1
26	10 6	6 7	2 3	5 3	0 83	4 4	13 2
28	9 2	6 9	2 0	5 8	1 10	4 6	13 6
29	8 8	5 5	2 7	3 7	0 89	2 9	7 8
26	7 6	5 2	2 1	3 5	0 64	2 8	10 0
26	7 9	5 2	2 0	3 3	0 40	2 9	9 9
34	9 7	4 2	1 4	3 1	0 35	2 8	11 4
33	9 9	4 0	1 6	2 7	0 49	2 3	11 8
32	8 5	5 3	2 3	3 4	0 66	3 0	19 0
38	10 2	5 4	2 3	3 8	0 69	3 1	3 0
52	10 7	5 5	2 7	3 4	0 71	2 7	3 6
56	10 7	6 0	2 5	4 0	0 50	3 5	2 4
38	10 9	7 3	2 4	5 4	0 83	4 5	6 2
61	10 4	7 3	3 1	4 9	0 84	4 1	3 5
60	10 3	7 6	3 6	4 8	0 81	4 0	4 7
32	11 8	5 3	2 7	3 3	0 89	4	5 0
25	14 2	6 0	3 0	3 8	0 78	3 0	8 0
43	13 0	5 6	2 2	4 1	0 87	3 2	2 2
45	13 0	5 6	2 1	4 1	0 77	3 4	14 0
46	13 0	5 1	2 3	3 6	0 83	2 8	2 2
38 2	10 2	5 8	2 06	4 2	0 64	3 7	8 3
41 6	10 8	5 8	2 24	4 1	0 69	3 4	9 4
44 9	9 33	5 9	1 20	4 2	0 62	3 6	8 2
>0 1	>0 1	>0 1	>0 1	>0 1	>0 1	>0 1	>0 1
>0 1	>0 025	>0 1	>0 1	>0 1	>0 1	>0 1	>0 1

1 second; F.E.V. Forced expiratory volume at 1 second; MBC Maximum breathing capacity; W.V. Walking ventilation; Terminal alv. N, per cent Terminal alveolar nitrogen percentage after 7 minutes of oxygen breathing

Table IV. Pulmonary function studies in patients in heart failure

Patient	Procedure	Before bronchodilators			After bron	
		V.C. (liters)	F.E.V (liters)	F.E.V (liters)	V.C. (liters)	F.E.V 1.0 (liters)
1	A	2 0	0 73	1 06	3 1	1 28
R R	B	2 3	0 85	1 20	3 2	1 07
2	A	1 1	0 31	0 52	1 2	0 32
H T	B	1 2	0 26	0 45	1 5	0 31
3	A	3 1	1 60	2 24	4 1	2 13
E L	B	3 0	1 99	2 34	3 6	1 98
4	A	2 6	0 75	1 30	2 7	0 70
L.M	B	2 8	0 65	1 21	3 1	0 74
5	A	2 5	1 07	1 64	3 2	1 68
M D	B	2 9	1 37	1 92	3 7	1 83
6	A	1 8	0 90	1 29	1 9	1 12
F T	B	1 9	1 00	1 37	1 8	0 96
Averages	A	2 18	0 89	1 34	2 70	1 21
	B	2 35	1 02	1 42	2 82	1 15
p Value	B	>0 05	>0 1	>0 2	>0 4	>0 2

A Control *B* One hour post-phlebotomy *V.C.* Vital capacity *F.E.V.* Forced expiratory volume at 1 second *F.E.V.* Forced residual capacity *E.R.V.* Expiratory reserve volume *R.V.* Residual volume *Terminal air N* per cent Terminal alveolar nitrogen

restoration of the circulating blood volume may be achieved so as to restore the lungs to the pre phlebotomy status, from both the hemodynamic and structural view points and therefore, to nullify the effects observed acutely after venesection

Summary

1 Hemodynamic and pulmonary function studies were evaluated in 15 patients with secondary polycythemia associated with chronic pulmonary emphysema.

2 The studies were made before and after acute venesection and again after sufficient venesection to maintain hematocrits at nearly normal levels for periods of 5 to 6 weeks.

3 Significant decreases in hematocrit, right atrial and right ventricular systolic, end-diastolic, and mean pressures, and significant increases in arterial oxygen saturation and tension oxygen consumption and arteriovenous oxygen difference were noted in measurements carried out 1 hour after the initial phlebotomy

4 In the total group, no changes occurred in pulmonary function studies after acute phlebotomy or repeat phlebotomies, or in hemodynamic studies after repeat phlebotomies

5 In patients with high end-diastolic right ventricular pressures at the initial catheterizations, acute phlebotomy was followed by decreases in the residual lung volume and functional residual capacity although these had increased to the control values after 6 weeks.

6 It is possible that the observed changes in O_2 gas studies and residual lung volumes may be related to changes in intrapulmonary blood volume or flow

7 All of the changes observed after repeated phlebotomies can be explained by the mechanical removal of red blood cells.

8 There is no indication that polycythemia of itself is detrimental to the hemodynamic or pulmonary function status of these patients when heart failure has not supervened.

9 Venesection has a therapeutic role in the management of patients with secondary polycythemia associated with chronic pulmonary emphysema. Immediate phlebotomy should be helpful in controlling heart

chodilators		T.L.C. (*liters*)	V.C. (*liters*)	*Recumbent lung volume*			Terminal alv. N (*per cent*)
F.E.V.₁ (*liters*)	*M.V.V.₁* (*L./min.*)			*F.R.C.* (*liters*)	*E.R.V.* (*liters*)	*R.V.* (*liters*)	
1 83	37	6 8	2 6	4 7	0 68	4 0	14 4
1 66	32	6 5	2 8	4 7	0 93	3 8	15 0
0 61	32	5 6	1 1	4 7	0 26	4 4	13 6
0 58	30	5 5	1 5	4 4	0 39	4 0	12 5
2 83	74	6 3	2 6	3 7	0 28	3 5	2 2
2 92	78	6 4	2 8	3 4	0 26	3 2	2 2
1 34	29	5 5	2 7	3 7	0 89	2 9	7 8
1 32	26	5 2	2 1	3 5	0 64	2 8	10 0
2 15	38	5 4	2 3	3 8	0 69	3 1	3 0
2 47	53	5 5	2 7	3 4	0 71	2 7	3 6
1 33	34	4 2	1 4	3 1	0 35	2 8	11 4
1 37	33	4 0	1 6	2 7	0 49	2 3	11 8
1 68	40 6	5 63	2 12	3 95	0 53	3 45	8 7
1 72	41 8	5 51	2 25	3 68	0 57	3 13	9 2
>0 5	>0 5	>0 1	>0 4	<0 01	>0 5	<0 005	>0 2

expiratory volume at 1 second. *M.V.V.* Maximum voluntary ventilation free. *T.L.C.* Total lung capacity. *F.R.C.* Functional ... percentage after 7 minutes of oxygen breathing

failure, and repeat phlebotomies, although not altering the hemodynamic or pulmonary function status of these patients, may be indicated because of the reduction in the viscosity and therefore, presumably for the effect on the incidence of thromboembolic complications. It would appear that the utilization of repeated phlebotomies should be determined by the degree of polycythemia rather than by the pulmonary function status of the patient.

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Aortic atresia and premature closure of foramen ovale

Myocardial sinusoids and coronary arteriovenous fistula serving as outflow channel

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In atresia of the mitral or of the aortic valve or of both together, blood from the left side of the heart escapes into the right atrium, usually through an interatrial communication. The interatrial communication is a true atrial septal defect or a peculiar type of secondary interatrial communication created by herniation and prolapse of the valve of the foramen ovale (septum primum) into the right atrial cavity.[1-7] The span of life of these patients, although always short, depends to some extent upon the size of the interatrial communication.[4]

Usually, the interatrial opening is small and, along with the fundamental valvular anomaly, is responsible for pulmonary venous obstruction.

Uncommonly, either the interatrial opening is smaller than average or there is premature closure of the foramen ovale[6,8,13] that precludes an opening between the atria. Under these circumstances, an alternate route for the escape of blood from the left atrium is present. This usually takes the form of anomalous connections between the pulmonary veins and the systemic venous system. A specialized form of such a connection is that in which a vein (known as the levoatriocardinal vein[9,11,13,14]) runs between the left atrium and a systemic vein.

Spolverini and Barbieri (cited by Walker and Klinck[14]), in a case of congenital aortic and mitral atresia with an almost complete closure of the foramen ovale, assumed that the pulmonary venous return was through the bronchial veins.

Among the 38 other cases of isolated aortic atresia that have been studied in our laboratory,[7] the major channel for egress of blood from the left side of the heart was at the atrial level in 33 instances (herniation of the valve of the foramen ovale into the right atrium in 21 cases, or atrial septal defect of one type or another in 12 cases).

In the other 5 cases there was a valvular

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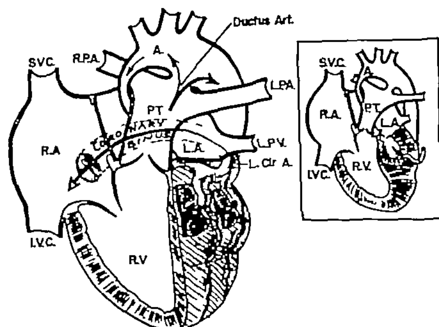


Fig. 1. Inset shows anatomic essentials in aortic atresia and premature closure of the foramen ovale. One of the two communications between myocardial sinusoids and the coronary arterial system which were observed in the case reported is shown. The main body of the illustration shows the anatomic features and the assumed direction of the flow of blood in the case reported. Blood returning to the left atrium from the lungs then flows into the left ventricle. The blood then flows through myocardial sinusoids to branches of the coronary arterial system. In the latter vessels the blood flows in a retrograde fashion to enter the left circumflex artery (L.Cir.A.). The latter vessel is in fistulous communication with the coronary sinus. Through this connection, pulmonary venous blood enters the coronary sinus and, finally, the right atrium (R.A.).

competent patent foramen ovale. In 3 of these a channel for egress of blood at the ventricular level was present in the form either of a single ventricle or a ventricular septal defect. In the other 2 of these latter 5 cases, uncertainty existed as to the route taken by the blood leaving the left side of the heart. In none of the 38 cases was there premature closure of the foramen ovale, and none exhibited a levoatriocardinal vein.

We have identified in the necropsy specimen of a 24-day-old male infant with aortic valvular atresia an intact ventricular septum and premature closure of the foramen ovale, evidence for a different route for the escape of blood from the left side of the heart. This is summarized diagrammatically in Fig. 1. Since the foramen ovale was sealed and since no pulmonary venous obstructions or anomalies were present, blood entering the left atrium from the pulmonary veins could flow only into the hypoplastic left ventricular chamber (the latter type of left ventricle is a characteristic of the heart in cases of aortic valvular atresia). Because the aortic valve was atretic, blood from the left ventricle could not flow forward in a normal direction. The mitral valve, although hypoplastic, appeared to be competent, allowing the left ventricular systolic pressure to rise to high levels. Numerous openings of myocardial sinusoids were present on the endocardial surface of the small left ventricle (Fig. 2). Through these sinusoids, it is assumed that blood from the left ventricle flowed toward the epicardium, where gross connections were identified between myocardial sinusoids on the one hand and the anterior descending coronary artery and a branch of the left circumflex coronary artery on the other.

These arteries were found to be grossly enlarged and tortuous (Fig. 3,a). In the left atrioventricular sulcus, the left circumflex coronary artery became continuous with the lateral extremity of the coronary sinus, providing an arteriovenous fistula. The



Fig. 2. *a*. Interior of the left atrium and left ventricle (*L.V.*). The pulmonary veins (*P.V.*) join the left atrium, of which the appendage (*A.A.*) is enlarged. No interatrial communication is present. The pitted effect of the endocardial surface of the left atrium represents ostia of Thebesian veins. The mitral valve is hypoplastic but basically normal. The left ventricular cavity is small. The left ventricular ostia of numerous myocardial sinusoids form the numerous depressions of the left ventricular endocardial surface. The left ventricular wall is hypertrophied. The enlarged right ventricle (*R.V.*) partly overlaps the left ventricle. *b*. Interior of left ventricle (*L.V.*) and section through a dilated myocardial sinusoid (*Sin.*). The latter runs between the left ventricular cavity and the lumen of the dilated anterior descending coronary artery (*A.D.*). Arrows indicate assumed direction of the flow of blood. The enlarged right ventricle (*R.V.*) partly overlaps the left ventricle. The pulmonary trunk (*P.T.*) is enlarged.

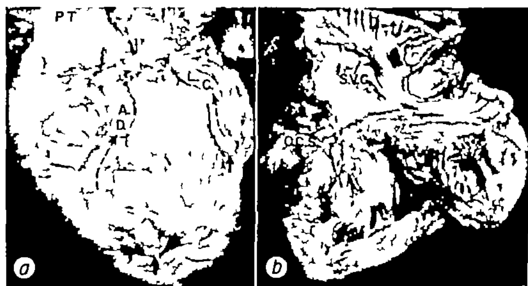


Fig. 3. *a*. Exterior of heart. The solid arrows indicate sites of gross communication of myocardial sinusoid with the anterior descending coronary artery (*A.D.*) and a branch of the left circumflex coronary artery (*L.C.*). The arteries were grossly dilated. The broken arrows indicate assumed direction of the flow of blood in these arteries toward a coronary arterial-coronary sinus fistula (see Fig. 1). The hypoplastic ascending aorta is hidden by a grossly enlarged pulmonary trunk (*P.T.*). *b*. Interior of right side of heart and exterior of enlarged coronary sinus (*C.S.*). *O.C.S.* Ostium of enlarged coronary sinus in right atrium. No interatrial communication. The probe (*S.V.C.*) is in the superior vena caval orifice.



Fig. 4 Photomicrograph of the lung. Dilated lymphatic vessels of visceral pleura and of interlobular septa. The picture is consistent with that of pulmonary venous obstruction. Elastic tissue stain ×20.

coronary sinus was dilated and its intima was fibrous (Fig. 3,*b*). It is assumed that blood which flowed from the left ventricle through myocardial sinusoids entered the two aforementioned coronary arterial branches. Flowing retrograde in these arteries, the blood then entered the main channel of the left circumflex artery from which it flowed into the coronary sinus, and then into the right atrium. From the latter chamber the blood entered the right ventricle, from which it was distributed to the pulmonary arteries and by "reverse flow" through the ductus arteriosus to the aorta.[10, 14-16]

Histologic examination of the lungs (Fig. 4) showed features of pulmonary venous obstruction in the form of dilatation of lymphatics and engorgement and tortuosity of capillaries.

Comment

Communication of the left ventricular cavity with coronary arteries through myocardial sinusoids is commonly observed in cases of aortic valvular atresia if the mitral valve is present and competent.[7] In the usual instance, however, wherein there is a route for the flow of blood from the left atrium either through an interatrial communication or through an anomalous vein escape of blood through myocardial sinusoids is not a vital phenomenon.

The unusual and unique feature of our case of aortic atresia is coexistence of a coronary arterial-coronary sinus fistula. In the presence of the premature closure of the foramen ovale, the anomalous connections of the coronary system provided a vital channel for the flow of blood from the lungs to the right atrium. The peculiar route for the flow of pulmonary venous blood in our case provided a thread upon which life depended. That this was an inadequate route, however, is evidenced by the fact that the lungs showed signs of extreme degrees of pulmonary venous obstruction and the infant died at an early age.

In pulmonary valvular atresia with intact ventricular septum and a competent tricuspid valve, some right ventricular blood may escape into the coronary arteries through myocardial sinusoids.[19-22] The phenomenon is comparable to circumstances in the left side of the heart when the aortic valve is atretic.

Summary

In a 24-day-old male infant with aortic atresia, intact ventricular septum, and premature closure of the foramen ovale, a complicated route for the flow of blood from the left side of the heart into the right atrium was interpreted as having occurred on the basis of pathologic findings. The route started in the left ventricular cavity and proceeded into myocardial sinusoids, which, in turn, communicated in the epicardium with two coronary arteries. A fistula between the left circumflex coronary artery and the coronary sinus provided the final link in the route, which terminated in the right atrium.

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Experimental and laboratory reports

Percutaneous subclavian catheterization of the right heart and pulmonary arteries

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A rapid simplified technique for right heart catheterization has been employed with success in this laboratory. It has proved to be especially valuable for use in difficult patients and in patients in whom it is desirable to avoid "cutdowns." This has been accomplished by the use of a standard 36-inch Bardic 17-gauge radiopaque Intracath passed via percutaneous right or left subclavian venipuncture. Through the use of this technique excellent pressure tracings and samples of blood were obtained in all areas of the right heart and pulmonary arteries, including the wedge position.

Wilson[1-3] has popularized the use of percutaneous subclavian venipuncture for monitoring central venous pressure and as a means of securing a vein for infusions. The many advantages of this technique and the pertinent physiology are well documented.[1-4] For these reasons it has replaced the "cutdown" in the management of seriously ill patients on our† services.

During the past 2 years, 412 standard 12-inch catheters have been placed in the superior vena cava via the subclavian approach. As demonstrated by pulse contour the catheter frequently passed into the right ventricle prior to withdrawal to the superior vena cava where it remained for purposes of monitoring and infusion. This technique is advantageous in the presence of (1) extreme obesity, (2) shock, and (3) obliteration of veins by previous use.

During the past year investigational work has been done[5] which required repeated heart catheterization in the same individual. It was often difficult to isolate veins for venotomy after the second or third catheterization. Difficulties encountered in passing cardiac catheters through the

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antecubital veins may be obviated by using this technique for cardiac catheterization.

Materials and methods

The equipment used for the procedure is simple and inexpensive a sterile 36-inch radiopaque Intracath with detached needle a 10-c.c. syringe with saline a syringe and needle filled with a local anesthetic a forceps and a rotating adaptor for attachment to the pressure transducer via the stopcock manifold The pertinent anatomy is demonstrated in Fig 1 Note the relationship of the subclavian vein to the clavicle subclavian artery and brachial plexus. Fig 2 further depicts the position of the subclavian vein its proximity to the artery and pleura and the path taken by the venipuncture needle The external landmarks for the procedure (Fig 3) are a point halfway between the anterior axillary fold and the acromion process and a point in the center of the triangle formed by the two heads of the sternocleidomastoid muscle as it joins the clavicle The venipuncture needle is advanced along the line which joins these points

The patient is placed in Trendelenburg's position to elevate the central venous pressure and thereby reduce the likelihood of air embolus. The skin is prepared with

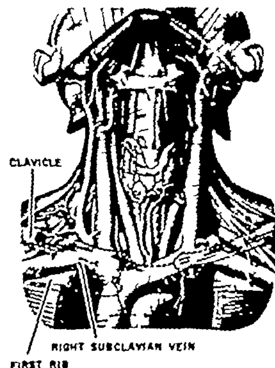


Fig 1 Illustration of regional anatomy Note the direct proximity of the subclavian vein to the posterior surface of the superimposed clavicle and consider the presence of only supportive structures (pectoralis major muscle subclavian muscle and/or costoclavicular ligament) between the skin and the vein. (From Sobotta Figge *Atlas of Human Anatomy* Vol. III Part 1 Fig 46, New York, 1964 Hafner Publishing Company by permission.)

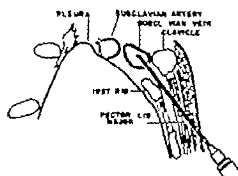


Fig 2 Right sagittal view of thorax at point of entry of the needle into the subclavian vein Note the simplicity of walking down the posterior surface of the clavicle into the subclavian vein (A more perpendicular approach predisposes to entry into the artery and/or pleura)

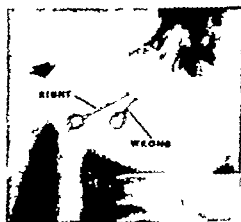


Fig 3 Photograph depicting the safe angle of advancement of the needle from the mid point between the anterior axillary fold and the acromion process (*arrows*) to the center of the triangle formed by the two heads of the sternocleidomastoid muscle



Fig. 4. Contrast medium injected via the median cubital vein. Note the large valves (*lower left arrows*) and the tortuous course of the distal veins bypassed by the catheter as it enters the subclavian vein (*middle arrow*), and the tip of the catheter in the superior vena cava (*right arrow*).

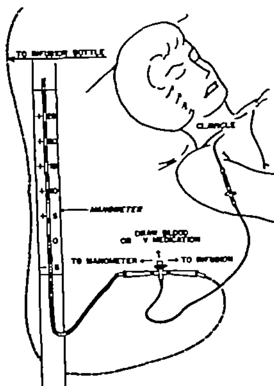


Fig. 5. Readily available arrangement for bedside monitoring. Note that a pressure transducer may be attached directly at the top of the 3-way stopcock via a 20-gauge needle for simultaneous recording of pressure and administration of fluid. Depicted is a most adaptable plastic stopcock and tubing. All connections must be taped to avoid obvious possible complications. The Intracath is taped to the subclavicular areas as with Intracaths used in peripheral veins. A hemostatic suture may be placed if the needle puncture causes cutaneous bleeding.

antiseptic solution* and the landmarks are noted. Local anesthetic may be injected along the path to be taken by the venipuncture needle, including the periosteum of the clavicle. Through the use of sterile technique, a 2-inch, 14-gauge, thin walled needle (separated from the standard Intracath set) is attached to a 10-c.c. syringe partially filled with saline. The needle is then inserted inferior to the clavicle according to the directions previously described. After cutaneous puncture, a small amount of saline is injected to insure continued patency of the needle. The needle is slowly advanced while negative pressure is applied through the syringe. Care is taken to avoid disturbing the external anatomy prior to advancement of the needle so that the motion of the catheter follows a straight line from skin to vein (Fig. 3). In this manner maneuverability of the catheter is excellent as the tortuous course from the arm to the heart is bypassed (Fig. 4). The needle is walked down the posterior surface of the clavicle while the syringe is kept adjacent to the chest wall. This aids in avoiding structures subjacent to the subclavian vein. Entry into the subclavian vein is indicated by a sudden free flow of blood. The needle is stabilized with the forceps, the syringe is disengaged, and the sterile 36-inch, 17 gauge Intracath is passed through the needle to the desired depth. The needle is withdrawn and the catheter advanced and manipulated in the usual manner. If the catheter fails to pass smoothly through the needle into the vein, a slight adjustment in the position of the needle may be necessary to assure that it has not inadvertently passed from the venous lumen. The cath

*Betadine Solution, Physicians Products Co., Inc., Petersburg, Va.

eter should not be withdrawn through the sharp needle since the tip of the catheter may be easily severed subcutaneously

The procedure has been done both with and without the nylon stylus in place The Intracath may be attached to a standard infusion set for the administration of fluids or to appropriate adaptors for purposes of monitoring pressure prior to insertion through the needle (Fig 5)

Discussion

This method provides a rapid catheterization technique Discomfort to the patient is decreased and quality tracings are obtained Ectopic premature contractions caused by this flexible lightweight catheter are rare Because of the size of the vessel venospasm is not encountered. When more specialized catheters are indicated they may be inserted using a flexible catheter guide [7]

Angiograms and postmortem studies have not demonstrated the formation of hematomas or vascular extravasation at the site of venipuncture Contrast medium was injected via the antecubital vein with a catheter in place (Fig 4) Note the valves in the basilic vein and the tortuous course of the cephalic vein which are bypassed by this procedure A repeat injection was made during a strenuous Valsalva maneuver simultaneous with removal of the catheter and further depicted no extravasation even with markedly elevated central venous pressure. Of the 412 patients, 17 have been studied at autopsy The site of venipuncture was often difficult to demonstrate, and again there were no hematomas. Histologically phlebitis was not observed In one patient who had intractable shock and congestive heart failure secondary to myocardial infarction a small 1 by 3-mm thrombus was noted at the tip of the catheter where it lay in the superior vena cava. No other complications have been noted at autopsy

Among the patients who survived their illnesses, only 4 suffered possible complications from the catheter despite constant use in several for over 2 months (1) One patient developed minimal inflammation at the site of skin entry after 2 weeks. This cleared spontaneously with removal of the catheter (2 and 3) Staphylococcal septicemia occurred in one patient while a catheter was in place. Prior to subclavian venipuncture, a septic course and a postoperative abdominal fistula with abscess formation were present She responded well to therapy Pneumococcal septicemia also was observed in one patient who had pneumococcal pneumonia. (4) In a patient with pulmonary metastatic choriocarcinoma the right subclavian artery was entered and the needle immediately withdrawn The left subclavian vein was then catheterized Eight hours later symptoms of a serosanguineous pleural effusion were noted The effusion was aspirated Two weeks later a repeat aspiration was undertaken when she again developed an effusion. She responded to methotrexate.* Because of the recurrence it seems unlikely that the first effusion resulted solely from the arterial puncture

By comparison considerable morbidity (28 per cent) has been reported in a recent article[8] describing direct percutaneous catheterization of the pulmonary artery Our method is far safer and more adaptable than this technique and capable of giving the same information. It is often desirable to obtain mixed venous blood repeatedly for laboratory study and to be able to perform catheterization of the pulmonary artery at the bedside in critically ill patients. The advantages inherent in performing any catheterization in the laboratory must be weighed when one is deciding to do a bedside procedure. With the monitoring of the pressure pulse contour as the only guide the subclavian approach has been used to position the catheter in the pulmonary artery Infusion at that area as well as the constant monitoring of pressure and aspiration of blood for laboratory studies, are easily accomplished by way of a three way stopcock.† In many of the patients in whom the 12-inch catheter was used venous pressure was monitored intravenous medication was given and blood was aspirated for laboratory studies without disturbing the patient The patients appreciated the comfort of only one venipuncture, despite weeks and months of hospitalization It appears that

*Lederle Laboratories, Pearl River N. Y.
†K-3L—3-way stopcock and extension tube, Pharmaseal Laboratories, Glendale Calif

this approach is far safer and more adaptable than that advocated in the report[8] previously noted

Summary

A simple, rapid inexpensive method of right heart catheterization using a disposable catheter has been presented. Sacrifice of a vein and scarring is avoided. Radiation of the patient is minimized because of prompt entry into the right ventricle and the ease of manipulation. Strict attention to every detail must be followed to avoid the previously reported complications.[1-4]

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Pulmonary venous responses to immersion hyperthermia and hypothermia

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Previous studies have shown that the pulmonary veins in intact dogs play an active role in the general hemodynamic adjustments to acute changes in circulating blood volume induced by hemorrhage and transfusion. The present studies were performed to learn the responses of the pulmonary circulation, particularly the pulmonary veins, in intact dogs to immersion in water baths of various temperatures.

Methods

Fifteen adult mongrel dogs weighing from 19 to 24 kilograms were divided into three groups of 5 animals each. One group was immersed in a water bath of 23°C, another group in a water bath of 14°C, and another group in a water bath of 40°C. The immersion was performed in a specially constructed tub so that the water covered the supine animal to a point just above the sternum, leaving only the head and neck, which were supported above the level of the water. Under such conditions the animals were subjected to a mean hydrostatic pressure of 140 mm. of H_2O.

Prior to immersion the animals were lightly anesthetized with urethane (1.5 Gm. per kilogram) and catheters were placed in the right atrium, pulmonary artery, small pulmonary vein, and left atrium. In addition, pressures were recorded directly from the femoral artery, from the intrapleural space, and from a small peripheral vein of the hind paw. All pressures were electronically integrated to yield mean pressure. Intrathoracic pressures were corrected for intrapleural pressure by subtracting intrapleural pressure from the observed intrathoracic vascular pressures.

The experimental procedure, including the method of catheterizing a small pulmonary vein transseptally, has been described in detail elsewhere.[1] The catheter in the small pulmonary vein was advanced into the wedged position and then withdrawn a few centimeters. Postmortem studies indicated that the catheter had been in a pulmonary vein that measured between 1.5 and 2.0 mm. in diameter. The zero reference for all pressures was taken at a level determined fluoroscopically to be the mid point of the right atrium.

Cardiac output was obtained by means of the dye-dilution method by introducing a known quantity of Cardiogreen dye into the pulmonary artery and measuring the concentration of the dye in blood withdrawn at a constant rate (34 c.c. per minute) from the left atrial catheter employing a Colson densitometer. Pul-

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monary blood volume was calculated from the dye-dilution curve according to the method of Hamilton and associates.[3]

After the animals were catheterized they were placed in an empty tub, and the zero reference was reset. After control pressures, cardiac output, and pulmonary blood volume were determined the tub was rapidly filled with water of the desired temperature. The temperature of the water-bath was maintained within ±2°C. of the desired temperature during the entire experimental period. Pressure, cardiac output and pulmonary blood volume were redetermined 2, 10 and 30 minutes after immersion. The tub was then emptied rapidly and measurements were again made 2 and 10 minutes after the animals had been exposed to ambient air.

Pulmonary vascular resistance (PVR) was calculated according to the formula

$$PVR = \frac{\overline{P}_{pa} - \overline{P}_{la}}{C.O.} \qquad (1)$$

where $\overline{P}_{pa}$ = mean pulmonary arterial pressure in mm. Hg, $\overline{P}_{la}$ = mean left atrial pressure in mm. Hg and C.O. = cardiac output in liters per minute.

Pulmonary venous resistance was calculated according to the formula

$$\text{Pulmonary Venous Resistance} = \frac{\overline{P}_{vs} - \overline{P}_{la}}{C.O.} \qquad (2)$$

where $\overline{P}_{vs}$ = mean small pulmonary vein pressure in mm. of Hg.

Systemic vascular resistance (SVR) was calculated from the formula

$$SVR = \frac{\overline{FA}}{C.O.} \qquad (3)$$

where $\overline{FA}$ = mean femoral arterial pressure in mm. of Hg.

These formulae express resistance in units which must be multiplied by 80 to be converted to dynes sec. cm.$^{-5}$

Packed red blood cell volume was measured for blood withdrawn from the pulmonary artery for each of the test periods indicated above. Esophageal temperature was monitored by means of a thermocouple.

Results

Immersion at 23°C. Immediately after the animals had been immersed in a water bath at 23°C., esophageal temperature decreased and continued to decrease during the entire period of immersion (Fig. 1). Removal of water from the tub was associated with an increase in esophageal temperature. However, 10 minutes after exposure of the animals to ambient air the esophageal temperature had not returned to control levels (Fig. 1).

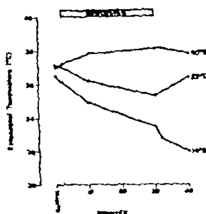


Fig. 1. Influence of immersion in water-baths of 23°C., 14°C., and 40°C. on esophageal temperature in intact lightly anesthetized dogs.

Immersion was associated with no change in femoral arterial or right and left atrial pressures, and with a slight increase in pulmonary arterial and small pulmonary vein pressure (Table I, Fig. 2). Intrapleural pressure increased by about 3 mm. Hg. Pressure in a small peripheral vein increased markedly (Table I, Fig. 2).

Cardiac output first increased and then decreased, whereas pulmonary blood volume decreased slightly, if at all (Table I, Fig. 3). Total pulmonary vascular resistance increased slightly, but there was essentially no change in pulmonary venous resistance. No change in systemic vascular resistance occurred until the end of the immersion period (Table I).

The time course of the relationship between pulmonary blood volume and pulmonary venous pressure is shown in Fig. 4. The relatively small loop indicates that the pressure-volume relationships (distensibility state) associated with immersion at 23°C. were only slightly altered. It is understood that the pressure-volume diagram shown in Fig. 4 is only an approximation of the true pressure-volume rela-

Table I Summary of the influence of immersion in water-baths of 23°C 14°C and 40°C on

Physiologic parameters	Neutral (23° C)				
	Control	Time after immersion (min)			
		2	10	30	40
Right atrial pressure (mm Hg)	4.5	4.3	4.7	4.5	4.3
Pulmonary arterial pressure (mm Hg)	22.8	24.2	23.9	23.4	22.7
Small pulmonary vein pressure (mm Hg)	14.4	15.1	15.3	14.8	14.3
Left atrial pressure (mm Hg)	4.3	4.3	4.7	5.2	4.1
Intrapleural pressure (mm Hg)	−3.9	+0.2	−0.1	−0.4	−3.1
Femoral arterial pressure (mm Hg)	102	104	97	97	102
Cardiac output (L min)	3.34	3.59	3.15	2.65	3.30
Pulmonary blood volume (c)	23	238	230	209	233
Systemic vascular resistance (units)	30.1	28.0	29.8	36.1	30.4
Pulmonary vascular resistance (units)	5.89	5.56	6.20	6.87	5.87
Pulmonary venous resistance (units)	3.14	3.15	3.59	3.62	3.10
Peripheral venous pressure (mm Hg)	6.7	10.2	12.0	9.7	7.0
Cardiac rate per min	172	172	159	146	152
Respiratory rate per min.	49	45	41	37	42
Esophageal temperature (degree C)	37.1	37.0	36.2	35.3	36.4
Hematocrit (	49	48	50	48	48

*The values represent the means for 8 lightly anesthetized dogs in each group.

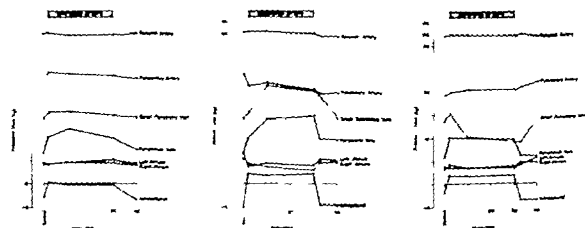


Fig 2 Influence of immersion in water-baths of 23°C (*left*), 14°C (*center*), and 40°C (*right*) on various pulmonary vascular pressures as well as on femoral arterial, peripheral venous (hind-paw), and intrapleural pressures in intact lightly anesthetized dogs

tionships or time course of the distensibility state. The method employed for determining pulmonary blood volume in these studies measures the blood volume between the catheter in the pulmonary artery placed just distal to the pulmonary valve and the catheter in the left atrium Because the major portion of the total pulmonary blood volume is within the pulmonary veins, it is reasonable to assume that changes in pulmonary blood volume reflect primarily changes in pulmonary venous blood volume. Another criticism of the pressure-volume diagram shown in Fig 4

*various physiologic parameters**

	Cold (14° C.)						Hot (40° C)					
	Control	Time after immersion (min.)					Control	Time after immersion (min.)				
		2	10	30	32	40		2	10	30	32	40
	5 5	4 4	3 6	3 0	4 6	4 7	3 7	3 5	3 5	3 9	4 8	4 6
	23 7	21 2	21 9	20 3	19 5	19 7	19 3	19 9	20 5	20 5	21 2	22 3
	14 1	15 4	21 2	20 0	18 5	14 1	13 9	15 2	10 2	9 4	9 3	14 5
	6 6	3 8	4 4	4 0	5 3	4 9	3 3	4 1	3 5	3 5	4 4	5 8
	−5 0	+2 1	+1 9	+2 4	−4 5	−4 6	−2 0	+1 8	+1 7	+1 8	−3 5	−3 6
	107	109	107	100	90	89	93	99	98	97	102	92
	3 63	4 21	3 54	3 01	2 73	2 29	3 45	4 42	4 40	4 68	4 19	4 46
	260	296	279	261	283	241	255	321	299	314	293	298
	29 8	34 6	30 8	33 5	33 2	38 5	33 4	28 3	24 6	25 7	27 6	21 7
	4 83	4 64	5 32	5 80	5 67	6 90	5 06	4 27	4 20	4 39	5 64	3 71
	2 11	2 94	4 51	4 66	4 09	3 48	3 34	3 18	1 40	1 46	2 54	1 96
	6 7	9 9	13 9	14 7	9 8	9 7	5 8	10 1	10 2	9 7	6 5	6 0
	162	178	174	182	180	188	181	173	190	186	198	190
	47	45	43	32	36	45	46	91	102	115	85	59
	38 5	36 1	34 9	33 5	32 8	32 0	37 0	37 2	37 8	38 1	38 1	37 8
	48	50	53	52	53	50	50	48	48	52	50	52

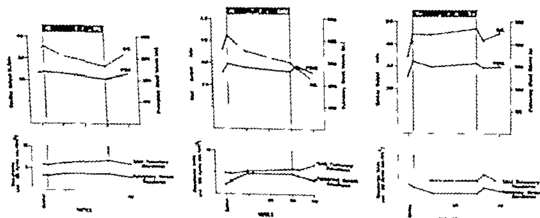


Fig. 3 Influence of immersion in water-baths of 23°C (*left*) 14°C (*center*), and 40°C (*right*) on cardiac output, pulmonary blood volume *total* pulmonary vascular resistance and pulmonary venous resistance in intact lightly anesthetized dogs.

is that the pressure measured in a single pulmonary vein may not reflect changes in pressure in the other pulmonary veins. However in previous experiments[8] in which catheters were placed in two small veins in different pulmonary lobes the changes in pressure were always consonant

After removal of water from the tub all pressures, resistances, cardiac output, and pulmonary blood volume returned to control levels (Table I Figs. 2 and 3)

No significant change in mean packed red blood cell volume occurred during the experiment (Table I)

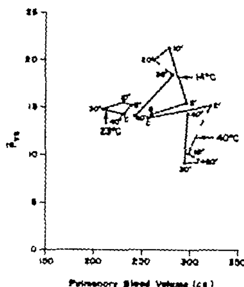


Fig. 4 Influence of immersion in water-baths of 23°C 14°C and 40°C on the relationship between mean pulmonary venous pressure and pulmonary blood volume in intact lightly anesthetized dogs. Broken lines represent the pressure-volume relationship during immersion, whereas solid lines represent this relationship after the water was withdrawn from the bath

Immersion at 14°C Immersion of the animals in a water bath at 14°C resulted in a marked decrease in esophageal temperature (Table I Fig 1) Esophageal temperature continued to decrease after removal of the water from the tub and exposure of the animals to ambient air (Table I Fig 1)

Immersion of the animals at 14°C resulted in a rise in intrapleural pressure of about 7 mm Hg Mean pressure in the small pulmonary vein increased whereas that in the pulmonary artery and left and right atria decreased (Table I Fig 2) The femoral arterial pressure did not change, whereas the pressure in the peripheral vein increased markedly (Table I Fig 2)

Cardiac output first increased and then decreased After a slight initial rise, pulmonary blood volume returned to control levels, where it remained during the entire period of immersion Total pulmonary and pulmonary venous resistance increased after immersion with the increase in pulmonary venous resistance being relatively greater than the increase in total pulmonary resistance (Table I Fig 3) Immersion was associated with an increase in systemic vascular resistance (Table I)

The time course of pressure volume relationships between the small pulmonary vein and the pulmonary blood volume are shown in Fig 4

After removal of the water from the tub and exposure of the animals to ambient air the pulmonary arterial left atrial and right atrial pressures remained below control levels whereas small pulmonary vein pressure returned to the control level (Table I Fig 2)

Cardiac output continued to decrease after removal of the water from the tub (Table I Fig 3) Furthermore although pulmonary venous resistance decreased toward control levels after the water had been removed total pulmonary resistance continued to increase (Table I Fig 3) Systemic vascular resistance also continued to increase after removal of the water from the bath (Table I)

Immersion at 40°C Esophageal temperature increased immediately after immersion of the dogs at 40°C and continued to rise for 10 minutes after immersion after which time it remained relatively stable (Table I Fig 1) Ten minutes after exposure of the animals to ambient air the esophageal temperature had decreased but was still above control levels (Table I Fig 1)

Immersion at 40°C was associated with a rise in intrapleural pressure of about 4 mm. Hg Small pulmonary vein pressure increased immediately and then decreased markedly whereas pulmonary arterial pressure and left and right atrial pressures remained essentially unchanged (Table I Fig 2) After immersion of the dogs at 40°C femoral arterial pressure did not change whereas peripheral venous pressure increased markedly (Table I Fig 2)

Immediately after immersion of the animals the cardiac output and pulmonary blood volume increased and remained elevated throughout the entire period of immersion (Table I Fig 3) Total pulmonary and pulmonary venous resistance decreased after immersion of the animals at 40°C with the pulmonary venous resistance decreasing relatively more than the total pulmonary resistance (Table I Fig 3) Immersion was associated with a

decrease in systemic vascular resistance (Table I)

The time course of the pressure volume relationships between the small pulmonary vein pressure and the pulmonary blood volume are shown in Fig 4.

After removal of the water from the bath and exposure of the dogs to ambient air the small pulmonary vein pressure returned to control levels, whereas pulmonary arterial left atrial and right atrial pressures, which had changed relatively little during the period of immersion increased to above control levels (Fig 2 Table I)

Cardiac output and pulmonary blood volume decreased after the water had been removed from the tub but remained above control levels. Ten minutes after removal of water from the tub the total pulmonary and pulmonary venous resistances were still below control levels (Table I Fig 3) A further decrease in systemic vascular resistance occurred after removal of water from the bath (Table I)

Discussion

The most remarkable aspect of this study was the behavior of the pulmonary veins Immersion of the animals in water of 23°C resulted in relatively slight change in small pulmonary vein pressure and pulmonary venous resistance. Immersion at 14°C resulted in a marked rise in pulmonary venous pressure due to active constriction and marked increase in tone of the pulmonary veins. That the pulmonary venous constriction was active is indicated by the fact that pulmonary venous pressure increased while pulmonary blood volume did not change significantly (Fig 4) Furthermore while pulmonary venous pressure was increasing left atrial pressure decreased. The increase in pulmonary venous pressure was associated with an increase in pulmonary venous resistance. Immersion at 40°C resulted in a marked decrease in small pulmonary vein pressure and tone The decrease in pulmonary venous pressure must have been due to both a decrease in tone and dilatation of the pulmonary veins because pulmonary venous pressure decreased while pulmonary blood volume increased and left atrial pressure remained unchanged

Immersion in a water bath at 3°C was associated with an immediate increase in pulmonary arterial pressure, small pulmonary vein pressure, and cardiac output However these increases were so slight as to be hemodynamically insignificant. Continued immersion at 23°C was associated with a progressive fall in cardiac output and a rise in total pulmonary resistance The immediate rise in cardiac output was probably due to the effect of the hydrostatic pressure of the water on the surface of the body This also accounted for the marked rise in peripheral venous pressure However with time increased intrapleural pressure resulted in a rise in pulmonary vascular resistance and a fall in cardiac output. Bondurant and associates[6] found that immersion in water or the inflation of a G suit resulted in a transient increase in central venous pressure (superior vena cava) and pulmonary blood volume (determined with radioisotopes) in man These changes occurred within 30 seconds of immersion after which time the central venous pressure and pulmonary blood volume returned to control levels In the present studies the changes in right atrial pressure and pulmonary blood volume after immersion of the animals were slight, but the water pressure due to immersion was not high Furthermore, no measurements were made until the animals had been immersed for 2 minutes. Obviously any changes which occurred before this time would have been missed Another possible explanation for the difference in the two studies is the fact that immersion of a conscious human subject in water may result in psychoneurogenic reflexes which modify the vascular responses

Immersion in a water bath of 14°C was associated with an immediate decrease in pulmonary arterial and left and right atrial pressures which persisted throughout the period of immersion. Cardiac output increased immediately after immersion of the animals and then decreased The hemodynamic changes associated with immersion at 23°C were thus modified by immersion at 14°C., in that the immediate transient rise in pulmonary arterial pressure observed at 23°C did not occur at 14°C In addition, whereas no immediate change in right and left atrial pressures occurred at 23°C these pressures de

creased at 14°C. Furthermore at 23°C, the total pulmonary resistance increased more than did pulmonary venous resistance, whereas at 14°C the pulmonary venous resistance increased more than did total pulmonary resistance. The basis for the decrease in pulmonary arterial pressure is not clear. Kuhn and Turner[5] immersed dogs in cold water and found no change in pulmonary arterial, right atrial, or pulmonary wedge pressures. As indicated above, the increase in pulmonary venous resistance was probably due to active constriction of the pulmonary veins. The constriction of the pulmonary veins was probably due in part to the action of cold blood on the veins. Thus, the increase in pressure was much greater at 10 minutes than at 2 minutes after immersion. Galletti and associates[6] observed that in hypothermic dogs the pulmonary vascular resistance increased when pulmonary blood flow was kept constant. They attributed the increased pulmonary vascular resistance to increased vasomotion secondary to the action of cold blood on the veins. Some of the increase in pulmonary venous resistance must also have been due to increased blood viscosity. In this regard, Lynch and Adolph[7] during direct observation of the blood vessels of the rat mesocecum found that increased resistance to flow during hypothermia was not associated *with any observable changes in the caliber* of the blood vessels. They concluded that the increased resistance during hypothermia was due to alterations in the blood rather than in the blood vessel wall. Barbour, McKay, and Griffith[8] described a reflex mediated through the hypothalamus and originating in chilled skin which results in a shift of fluid from the blood vessels to the interstitial spaces, eventuating in an increase in hematocrit. In the present experiments a 10 per cent increase in hematocrit occurred after immersion of the dogs at 14°C (Table I). The influence of increased hematocrit on blood viscosity is well known.[9] Furthermore, the effect of hematocrit on viscosity becomes greater as shear rate decreases.[9] Thus in the present experiments the combination of increased hematocrit and decreased rate of blood flow must have acted to increase blood viscosity and in turn increase pulmonary vascular resistance. However, it is not likely that the great increase in pulmonary venous pressure which occurred after immersion of the animals was due entirely to the effect of increased blood viscosity.

Immersion at 40°C was associated with a decrease in small pulmonary vein pressure, total pulmonary vascular resistance, and pulmonary venous resistance and an increase in cardiac output and pulmonary blood volume. The hemodynamic responses observed during immersion at 23°C were modified by immersion at 40°C in a manner consistent with previous observations on the influence of a hot environment on the cardiovascular system.[11] It is interesting that the pulmonary veins respond to heat in the same manner as the peripheral veins, i.e., by a decrease in tone.

The peripheral venous pressure increased in each experiment. However, the increase in pressure was greater during immersion at 14°C than at 23°C and less at 40°C than at 23°C. These findings provide indirect evidence that systemic peripheral venous tone was increased by cold and decreased by heat.

Summary

The most significant aspect of these studies is the observation that the pulmonary venous responses to immersion in *neutral, hot, and cold water are similar* to those which would be predicted from knowledge of the behavior of the peripheral veins. Little information on pulmonary venomotor activity is available for intact animals. However, changes in the distensibility characteristics of the pulmonary veins in response to both physiologic and pathologic stimuli must be taken into consideration when appropriate, in the interpretation of hemodynamic phenomena.

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Mechanical alternans and the staircase phenomenon in dog papillary muscle

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The relationship of the interval between beats to myocardial contractility has aroused interest ever since 1871 when Bowditch[1] described the stepwise increase in the strength of contractions of frog ventricle which occurs when stimulation is begun after a period of rest ("staircase" or *Treppe*). More recently, studies on interval-strength relationships in cardiac muscle have been extended to include those which occur in mammalian preparations.[2-4] Mechanical alternans, described by Traube[5] in 1872 and characterized by the regular alternations of weak and strong contractions, appears to reflect an unusual interval-strength relationship, in that the alternation in contractility occurs without any accompanying alternation in the duration of the interval between successive contractions.

During a series of experiments aimed at elucidating the causative mechanism of mechanical alternans some evidence was obtained which appears to support a hypothesis that interval-strength relationships as reflected by the "staircase phenomenon"[1] are modified during the occurrence of mechanical alternans.

Methods

Unselected dogs, weighing between 5 and 10 kilograms, were anesthetized with intravenously administered sodium pentobarbitone (Sagatal†). Papillary muscles approximately 10 mm. in length and 1 mm. in width were rapidly excised from right ventricles and immediately immersed in 30 ml. of aerated Tyrode solution (composition in millimoles: NaCl, 130.02; KCl, 5.63; $CaCl_2$, 1.08; $NaHCO_3$, 28.00; glucose, 11.10; sucrose, 13.15; NaH_2PO_4, 9.10) prepared from analytical reagent-grade chemicals dissolved in all-glass distilled water. Thin strips of muscle were selected deliberately in an attempt to avoid the presence of poorly oxygenated fibers. The Tyrode solution was continuously aerated with 95 per cent O_2 + 5 per cent CO_2 and maintained at 35.0°C., unless otherwise stated. Isometric conditions were maintained by applying a constant resting tension of 2.5 grams. The muscles were stimulated with suprathreshold rectangular pulses of 10-msec. duration delivered from a Tektronix pulse generator Type 161 at the rate of 60 pulses per minute, unless otherwise stated. Large Ag-AgCl plate

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electrodes flanked the muscle on either side. Isometric contractions were detected with an RCA 5734 transducer the output of which was amplified as required displayed on a cathode-ray oscilloscope Tektronix Type 502 and photographed directly With the use of these experimental conditions, tensions ranging between 5 milligrams and 20 grams could be displayed as full-scale deflections on the oscilloscope

Transmembrane resting and action potentials were recorded from similar isometrically contracting papillary muscle preparations which were stimulated by means of a KCl filled microelectrode (resistance of 50-100 kilohms) instead of the Ag AgCl plate electrodes mentioned above. Transmembrane potentials were measured by the microelectrode technique of Ling and Gerard [4] using glass microelectrodes filled with 3 M KCl and having a resistance of 30 to 50 megohms. The stimulating and recording electrodes were placed approximately 1 cm. apart. The validity of the measuring and recording apparatus was checked by inserting a 100-mv signal between the recording microelectrode and the earth. Action potentials were displayed on a Tektronix 502 oscilloscope and photographed directly

Preparations were equilibrated in Tyrode solution for 30 minutes prior to the beginning of each experiment. The staircase phenomenon was produced when required by inserting a rest pause in a series of otherwise regularly spaced contractions.

Results

Mechanical alternans Spontaneously occurring mechanical alternans was recorded from 28 isometrically contracting papillary muscle preparations of the dog right ventricle stimulated with either the large Ag AgCl plate electrodes or a single KCl-filled glass microelectrode as described above Contractions recorded from a typical preparation with mechanical alternans are shown in Fig 1 The phenomenon persisted throughout approximately 60 minutes of immersion in Tyrode solution at 35°C after which the contractions gradually became regular in amplitude Lowering the temperature of the Tyrode solution from 35 0 to 37 0°C resulted in mechanical alternans that persisted for a significantly longer (p= 0 01) period of time, sometimes extending to 3 hours raising the temperature to 38°C had the reverse effect, in that it accelerated the rate at which the phenomenon disappeared. In any preparation the tension developed during the regular contractions which ultimately replaced the alternately weak and strong contractions of mechanical alternans was intermediate between that developed during the previously recorded weak and strong contractions. In such preparations, in which the alternately weak and strong contractions had spontaneously given way to contractions of regular magnitude, continued electrical stimulation after the insertion of a rest pause repeatedly resulted in the temporary restoration of mechanical alternans.

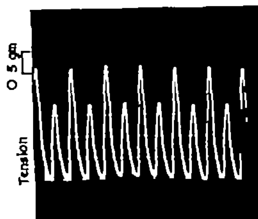


Fig. 1 Typical isometric contractions of a dog papillary muscle preparation with mechanical alternans. Rate of stimulation, 60 pulses per minute. Ag AgCl plate stimulating electrodes.

Increasing the rate of stimulation from 60 to 90 pulses per minute failed to abolish mechanical alternans in any of the above mentioned preparations reducing the stimulation rate from 60 to 25 pulses per minute resulted in its disappearance In this latter case return to stimulation at the rate of 60 pulses per minute was accompanied by the return of the phenomenon

Some papillary muscle preparations beat spontaneously and in 5 such preparations, mechanical alternans was observed in the absence of any applied electrical stimulation

Fig 2 which displays two successive con-

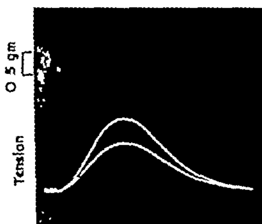


Fig 2 Type I successive isometric contractions recorded from papillary muscle preparation with mechanical alternans Amplifier gain constant Rate of stimulation 60 pulses per minute

tractions recorded from a typical papillary muscle preparation with mechanical alternans shows that the time taken to reach peak tension during contraction and the total duration of the contraction were the same for the strong as for the weak contractions. Fig 2 also shows that mechanical alternans at least in the dog isolated papillary muscle preparation need not necessarily be associated with an alteration of the end-diastolic resting tension the resting tension apparently being the same for weak and strong contractions alike Other experiments in which the sensitivity of the recording was greatly increased (10-milligram tension being displayed as a full scale deflection on the cathode ray oscilloscope) in order to enable detection of very small changes in resting tension failed similarly to indicate any correlation between the presence of mechanical alternans and an alternation in the end-diastolic resting tension However in several preparations it was noted that the weaker contractions sometimes were associated with an increased resting tension

Transmembrane resting and action potentials were recorded from 12 electrically stimulated preparations with mechanical alternans and in each case the cells to be impaled were chosen at random but were necessarily located on the surface In all of the 12 preparations the repeated finding was that mechanical alternans was not accompanied by electrical alternans In the impaled cells The magnitude of the transmembrane resting potential and the magnitude and the duration of the action potential remained constant and showed no evidence of alternation despite the presence of alternately weak and strong contractions

Isometric contractions recorded from a typical preparation with mechanical alternans immediately after the insertion of a rest pause in a series of otherwise regularly spaced stimuli are displayed in Fig 3 in which it is shown that the tension developed during the third contraction after the pause exceeded that developed during the second contraction but was less than that developed during the first contraction. Similarly the tension developed during the fifth contraction after the pause was greater than that developed during the fourth contraction but was less than that developed during the third contraction Consideration of the data displayed in Fig 3 shows that the contractions can be arranged into two groups one group, comprising the first, third and fifth contractions, shows a decline in the tension produced during successive contractions and the other group consisting of the alternate contractions, shows a progressive increase in the tension produced during

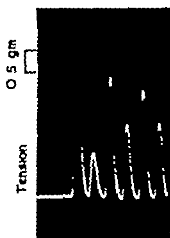


Fig 3 Six successive isometric contractions (1-6) recorded from a papillary muscle preparation with mechanical alternans after the insertion of a rest pause in a series of otherwise regularly spaced contractions. Rate of stimulation 60 pulses per minute Amplifier gain constant

successive contractions. This phenomenon was observed repeatedly after the insertion of a rest pause in a series of otherwise regularly spaced contractions of dog papillary muscle preparations with mechanical alternans. Whether the rest pause followed a weak or strong contraction apparently made no difference in that the tension developed during the first contraction after the pause always exceeded that developed during the second contraction, which in turn was less than that developed during the third contraction as described above. Studies of transmembrane potentials showed that the resting potential was constant for all the cells impaled and that the magnitude and duration of successive action potentials recorded from either the same or different cells remained constant despite the marked variation in the tensions produced during successive contractions.

Discussion

During the present study it has been shown that when stimulation of dog papillary muscle preparations with mechanical alternans was resumed after the insertion of a rest pause in a series of otherwise regularly spaced stimuli, the contractions recorded can be divided easily into two groups, one group showing a stepwise *decrease* and the other group a stepwise *increase* in the tension produced during successive contractions. These two opposite *trends* in contractility are displayed in alternate contractions of the same preparation, as was shown in Fig. 3 and contrast with the classic "staircase" or *Treppe* phenomenon—the progressive increase in tension produced during successive contractions after the insertion of a rest pause in a series of otherwise regularly spaced contractions —recorded from similar preparations without mechanical alternans. It is possible therefore that mechanical alternans is associated with an abnormal interval-strength relationship.

Why alternate contractions of a preparation with mechanical alternans should display such a divergence in contractile behavior after a rest pause is not clear. Studies of transmembrane potentials failed to provide any evidence to support a hypothesis that such a pattern of contractile behavior reflects a changed state of electrical excitation at least in the impaled surface cells. The graded series of contractions recorded after the rest pause was not associated with changed transmembrane resting or action potentials, a finding which suggests that the altered pattern of contractions reflects a change at the level of excitation-contraction coupling[7] rather than an altered pattern of excitation.

Throughout this study mechanical alternans was found to occur without any accompanying electrical alternans. However it is possible that if all the cells had been impaled electrical alternans might have been recorded together with mechanical alternans. The cells available for impalement necessarily were located on the surface of the papillary muscle preparation and therefore were well supplied with oxygen. The present results do not provide any information about electrical events in the cells which were away from the surface of the muscle and which therefore might have been poorly oxygenated. However the use of thin muscle preparations, of 1 mm in diameter should have ensured that all the cells of the preparation were adequately oxygenated. Other workers[8] similarly have failed to record electrical alternans from some preparations which displayed mechanical alternans. Hogancamp and associates[9] reported that in their experiments on the guinea pig ventricle electrical alternans was displayed by only one third to two thirds of the cells impaled in any single heart. If as the present findings indicate mechanical alternans sometimes may occur in the absence of any accompanying electrical alternans, then it is possible to envisage a system whereby mechanical alternans can result from a disturbance of either excitation or excitation-contraction coupling. In the latter case the disturbance could possibly reflect a changed metabolism such that the balance between the rate at which energy was used during a particular contraction and the rate at which energy was resynthesized prior to the arrival of the next excitatory stimulus was lost a condition which might result in different numbers of fibers entering into successive contractions.

The alternately weak and strong contractions characteristic of mechanical alternans cannot be attributed to an altered

rate at which the excitatory stimulus is propagated throughout the muscle. Mechanical alternans occurred whether the preparations were stimulated by means of large Ag-AgCl plate electrodes or a single KCl-filled microelectrode. Mitchell and associates[10] investigated mechanical alternans in dog papillary muscle preparations and concluded that the alternation in contractile strength resulted from alternating end-diastolic fiber lengths. In the present study alternation occurred apparently without any accompanying changes in end-diastolic tension. It seems likely, therefore, that mechanical alternans may result from a variety of causes.

Summary

Spontaneously occurring mechanical alternans in dog papillary muscles was investigated. Studies of transmembrane potentials indicated that mechanical alternans occurs, at least under the above-mentioned experimental conditions, without any accompanying electrical alternans. Perfusion at reduced temperatures favored the persistence of mechanical alternans. When stimulation was resumed after the insertion of a rest pause in a series of otherwise regularly spaced contractions, the resultant contractions separated readily into two groups, one group showing the positive inotropic effect and the other group the negative inotropic effect of activation.

We are deeply indebted to Dr. T. E. Lowe for his advice and critical comments in regard to this study.

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Percutaneous myocardial biopsy

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The diagnostic inaccessibility of the whole spectrum of cardiomyopathies requires that techniques of myocardial biopsy be further explored. This communication deals with observations in this laboratory of the following aspects of percutaneous myocardial biopsy: safety of the procedure, adequacy of tissue specimen for histologic study, significant complications, and permanent sequelae.

Materials and methods

Twenty mongrel dogs which weighed between 3.6 and 14.5 kilograms were studied under intravenous sodium pentobarbital anesthesia (22 mg. per kilogram). The procedure was monitored with a direct-writing Sanborn electrocardiographic recording of the standard and augmented limb leads before and immediately after the biopsy. During the biopsy, the needle itself served as an exploring epicardial electrode by way of a specially constructed connector (*vide infra*). This provided an instantaneous signal of epicardial contact. In some cases an electrocardiogram was obtained 7 days after the procedure, in order to evaluate residual myocardial damage.

Two types of biopsy needles were used: Franklin's modification of the Vim-Silverman needle[1] (FVS needle, 14 gauge × 110 mm.) and the Menghini needle[2] (1.6 × 70 mm.).

The former needle was modified by a special adapter (Fig. 1) which served initially as an electrode connector and also to limit the penetration of the cutting piece to 1.1 cm. beyond the trochar. Subsequently, Menghini needles were primarily used, and toward the end of the study were fitted with the special platinum connector similar to that reported by Hurst and associates[3] for electrocardiographic sensing (Figs. 2 and 3).

After the anesthetized animal had been

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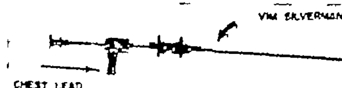


Fig. 1. Standard Vim-Silverman needle (14 gauge × 110 mm.) fitted with Luer-Lok adapter to limit penetration of the cutting piece 1.1 cm. beyond the trochar and to serve as an electrode connector for electrocardiographic epicardial sensing.

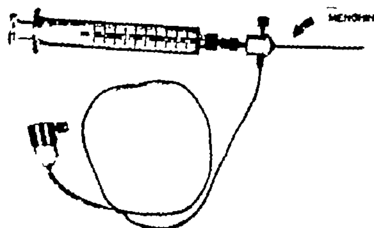


Fig. 2. Menghini biopsy needle (1.6 × 70 mm.) and syringe mounted with a special autoclavable platinum ECG electrode extension which serves also to limit penetration of the needle. See text.

placed in a right lateral decubitus position the needle was introduced through a tiny incision in the skin to the subcutaneous level at the point of maximal apical impulse and directed posteriorly, medially, and superiorly. Epicardial contact was signaled not only by touch but also by the electrocardiographic observation of marked S-T elevation of the injury type (Figs. 4 and 5). At this point the obturator was replaced by the cutting piece when the VS needle was used, and a biopsy specimen *was obtained in the usual fashion.* When the Menghini needle was used, the sheath of platinum connector which encases the needle was fastened 1.5 cm. from the skin when epicardial contact was established. Suction was then applied directly by a 10-c.c. syringe after the injection of 0.5 c.c. of normal saline to remove extraneous tissue from the needle. The needle was then advanced up to the restraining sheath and quickly removed from the chest.

Two to seven biopsy specimens per animal were obtained in this fashion from the free wall of the left ventricle at its apical extreme. The specimens were fixed in Zenker's 5 per cent acetic acid for a period of 2 to 6 hours. They were washed overnight in running water and placed in 70 per cent alcohol for 8 hours. Specimens were then processed in the routine manner and stained with hematoxylin and eosin.

All animals were sacrificed 2 weeks after biopsy.

Results

Table I summarizes the needle biopsy experience in 20 dogs. Specimens that were adequate for histologic analysis were obtained in all but 2 animals (Dogs 2 and 11) without major incident. Several animals became hyperpneic after the procedure, presumably as a result of pneumothorax. This complication was not confirmed by x-ray examination, however, because the

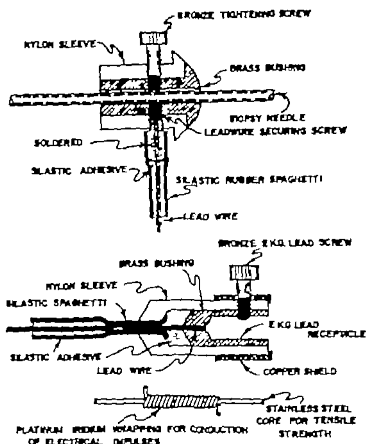


Fig. 3. Schematic diagram of the platinum electrode extension in Fig. 2.

respiratory change was transient. Except for 2 dogs allegedly dying of distemper (Dogs 3 and 7 at 13 days and 48 hours respectively) all survived the procedure until sacrificed at 14 days. Of 71 attempted biopsies (2 to 7 per animal) 43 yielded a satisfactory specimen (60.5 per cent). Twenty two of 30 attempts with the Vim-Silverman needle were successful (73.4 per cent) as compared with 21 of 41 attempts with the Menghini device (51.2 per cent). Toward the end of the study however experience with the Menghini needle was better and the general impression was that this needle was superior in terms of greater handling ease and less trauma to the subject.

Electrocardiographic phenomena in addition to marked S-T segment elevation on epicardial contact included a variety of arrhythmias, usually ventricular ectopic beats. One animal developed a ventricular

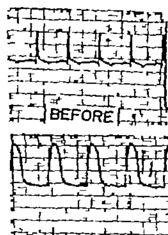


Fig. 4. Marked elevation of the S-T segment (precordial needle electrode) signaling contact of the needle with the parietal pericardium. Note the prebiopsy S-T segment elevation consistent with the histologic evidence of pericarditis in Fig. 7 (Dog 10).

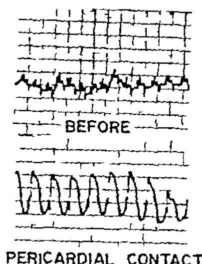


Fig. 5. Marked elevation of S-T segment (precordial needle electrode) signaling contact of the needle with the visceral pericardium (Dog 17).

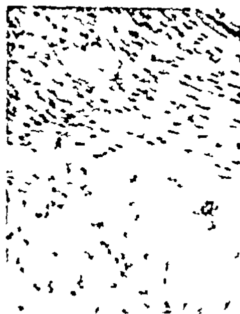


Fig. 6. Representative normal canine myocardial tissue obtained percutaneously with a Vim-Silverman needle. Hematoxylin and eosin stain. ×100.



Fig. 7. Myocardium and visceral pericardial tissue obtained with a Menghini needle showing mononuclear and polymorphonuclear leukocytic infiltration (Dog 10). See Fig. 4. Hematoxylin and eosin stain. ×100.

tachycardia which was still intermittently present 7 days later. Conduction disturbances and T wave changes were frequently noted immediately after the procedure but in most cases the electrocardiogram was within normal limits at 7 days. No persistent defects in QRS morphology were noted.

All animals which survived 14 days were sacrificed. In none was there evidence of the accumulation of pericardial fluid. Most had an adhesive pericarditis at the sites of puncture, limited to an area no greater than a square centimeter. Two of the 5 hearts which were further studied by gross sectioning revealed linear transmural scarring at or near the apex of the left ventricle. No gross coronary vascular defect was seen.

The biopsy specimens were analyzed for histologic and diagnostic adequacy. Satisfactory biopsies were obtained in 18 of 20 animals. All contained myocardial tissue (Fig. 6). Pericardium was identified in 4 and endocardium in one, although the left ventricular cavity was entered in 5 animals. Arterioles were identified in 13, a small artery in one and a large artery in another. One specimen verified an electrocardiographic diagnosis of pericarditis made prior to biopsy (Figs. 4 and 7).

Discussion

Experience with percutaneous needle biopsy of the heart has rarely been reported until Bercu's[4] recent study of Menghini needle biopsy of human myo-

Table I. Needle biopsy experience with 20 dogs

Dog number	Weight* (lb)	Vim-Silverman		Menghini		TA	TR	Histologic adequacy	E	M	P	Postmortem	Remarks
		A†	R	A	R								
1	13	4	2	0	0	4	2	+	−	+	−		
2.	8	0	0	2	1	2	1	−	−	−	−		
3.	13	2	2	0	0	2	2	+	−	+	−		Possibly died of distemper
4	12	0	0	2	1	2	1	+	−	+	−		
5	15	0	0	4	1	4	1	+	−	+	−		
6.	16	3	2	2	1	5	3	+	−	+	−	106 grams, negative	
7	30	4	2	1	0	5	2	+	−	+	−		Possibly died of distemper
8	25	4	2	2	1	6	3	+	−	+	−		
9	30	2	2	0	0	2	2	++	−	+	−	153 grams, few areas of adhesions, and scarring in LV near apex	
10.	25	1	1	2	2	3	3	+	−	+	+		Pericarditis
11	19	0	0	7	3	7	3	−	−	−	−		
12	16	0	0	6	2	6	2	+	−	+	±	92 grams, scar over RV	
13	24	0	0	3	2	3	2	+	−	+	−	176 grams, adhesion over LV and scar	
14	26	2	2	0	0	2	2	+	−	+	−		
15	32	2	2	0	0	2	2	+	−	+	−	160 grams, negative	
16	27	2	1	0	0	2	1	+	−	+	−		
17	24	0	0	3	3	3	3	+	−	+	−		
18.	19	0	0	5	2	5	2	+	−	+	+	144 grams, negative	
19	16	4	4	0	0	4	4	+	−	+	+		
20.	16	0	0	2	2	2	2	+	−	+	−		

*Total cardiac weight.
†A, Attempted biopsies; R, Biopsies yielding usable tissue; TA, Total biopsies attempted; TR, Total biopsies yielding usable tissue; E, Endocardium; M, Myocardium; P, Pericardium.

cardial septum, the work of Sutton and Sutton[6] with the Terry needle and that of Decourt[8] using an 18T BD needle. These reports are particularly encouraging in demonstrating the potential success of such a procedure in a substantial number of human subjects. In the past, most biopsy techniques were performed either through an open chest, as originally reported by Sutton and associates,[7] in human beings or after surgical fixation of the heart to the chest wall (Casten-Marsh technique[5]). In 1955 Price and associates described a percutaneous technique of obtaining canine cardiac tissue with a Vim-Silverman needle, but few details in regard to the clinical and electrocardiographic residue and the frequency of successful biopsy were mentioned. The techniques used in the current study are similar, but additional experience with a Menghini needle is also described and, to our knowledge, constitutes the first report of obtaining tissue from the free wall of the left ventricle with this device and technique.

It is evident that repeated puncture of the apical portion of the free left ventricular wall can be accomplished with safety, at least in dogs. Bleeding and tamponade are not problems, nor is pneumothorax when proper precautions are taken. There does not appear to be a significant hemodynamic alteration after this procedure, at least clinically, nor as a rule are there permanent electrocardiographic changes.

Tissue suitable for histologic analysis can be obtained in almost every instance, although several biopsy attempts may be necessary. This, however, is tolerated quite well.

Summary

A percutaneous technique for obtaining cardiac tissue with both Franklin Vim Silverman and Menghini needles is described Seventy-one biopsies were attempted in 20 dogs with cardiac tissue satisfactory for histologic analysis being obtained in 43 instances (60 5 per cent) Although the yield of specimens was higher with the FVS needle the general impression toward the end of the study was that the Menghini needle was a more facile device in terms of ease of handling and less trauma to the subject Cardiac tissue was obtained in 18 of 20 animals all specimens consisted of myocardium 4 of pericardium and 1 of endocardium

All but 2 of 20 dogs were sacrificed 14 days after biopsy No accumulation of pericardial fluid significant scarring or damage to the coronary arteries was demonstrated

The conclusion is that cardiac tissue suitable for histologic analysis can be safely obtained from the free wall of the left ventricle at least in dogs, utilizing a percutaneous needle biopsy technique even though several attempts may be necessary

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Inhomogeneous conduction in the A-V node

A model for re-entry

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Re-entry of a cardiac impulse has long been implied but never directly proved as a possible mechanism in the genesis of ectopic rhythms.[1,2] In 1913 Mines[3] observed in frogs and rayfish alternation of the contraction wave between auricle and ventricle and termed it "reciprocating rhythm." Two years later White[3] first described the clinical counterpart of this rhythm. Following these reports, numerous clinical and experimental studies have demonstrated reciprocal beating which has been considered to be a most likely example of re-entry. An extensive and critical analysis of these arrhythmias was published recently by Scherf and Cohen.[4]

In 1924 Drury observed that a reciprocal beat was seen only when conduction through the junctional tissues was strained to a critical point and suggested that the impulse traveled retrograde by only a certain number of fibers. The remainder of the fibers were refractory at that time but later recovered to conduct the impulse back to the ventricles. Experimental studies by Schmitt and Erlanger and later by Ashman and Hafkesbring utilizing isolated muscle strips, suggested that unidirectional block in some fibers caused re-entry.

Furthermore, Scherf and co-workers[1,1] argued that the stimulus conducted from the atrioventricular node back to the atria could not utilize exactly and exclusively the same path on its return to the ventricle and hence one must assume that at least the upper part of the conduction system was divided longitudinally into two paths. Clinical observations by Pick and Langendorf[10] led them to conclude that the prerequisites for reciprocal beating were (a) unequally depressed regions of the A-V junction engendering delayed retrograde conduction of a nodal impulse over fibers with less marked depression and unidirectional block in fibers with more marked depression and (b) return of the impulse from above into fibers which were blocked for retrograde conduction. These authors further postulated that two or more re-entries occuring in succession would not necessarily have similar pathways or rates of conduction. Finally, Moe and co-workers,[1,12] and Rosenblueth[13] and Kistin[14] independently presented evidence for dual or multiple functional pathways in the A-V transmission system and linked these findings to the phenomenon of reciprocation.

There appears to be general agreement that reciprocal beats are engendered by a re-entry movement which probably is

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caused by functional division of part of the conduction system into two or more pathways. However, previous experimental studies of reciprocal rhythm have failed to demonstrate the actual pathway of the re-entrant impulse. Hence ultramicroelectrode techniques were adopted to reveal the electrical activity of fibers and to plot the pathway of re-entry. Furthermore, the atrioventricular junction afforded a unique and accessible region of the specialized conducting tissues to test the re-entry model.

Method

Evidence of inhomogeneous conduction within the A-V junction was observed in isolated perfused rabbit hearts, during the course of electrophysiologic studies on A-V transmission in 98 experiments. Rabbits were anesthetized with intravenous pentobarbital sodium (30 to 35 mg. per kilogram). The chest was opened and the entire heart was quickly isolated. Perfusion of the coronary system was immediately started through an L-shaped glass cannula inserted into the ascending aorta with the use of an Anderson heart perfusion apparatus. The perfusate utilized was a modified Chenoweth's solution (K = 4.5 mEq. per liter); its temperature was maintained at 37 ± 1°C. throughout the experiments. The solution was constantly bubbled with 95 per cent O_2 plus 5 per cent CO_2, and the perfusion pressure was maintained at 60 cm. H_2O. The heart was suspended horizontally within a metal ring 15 cm. in diameter by several silk sutures. The ventricular surface was covered by a moist gauze sponge to prevent drying. An incision of 7 or 8 mm. was then made through the right atrium along its posterior junction with the right ventricle, exposing the ostium of the coronary sinus and the atrioventricular junctional tissues.

A ventricular electrogram was recorded between a needle electrode inserted into the left ventricular cavity and a surface electrode attached to the epicardium of the right ventricular apex. A small bipolar electrode with an interelectrode distance of 0.5 mm. was attached to the roof of the coronary sinus to record an atrial electrogram. Two flexibly mounted glass microelectrodes were simultaneously impaled into two different areas of the A-V junctional region to record transmembrane resting and action potentials from the specialized conducting fibers. Voltages were amplified through a neutralized input capacity amplifier and Tektronix type D and M amplifiers and displayed on two Tektronix type 532 oscilloscopes. Curves were photographed from one oscilloscope with a DuMont type 321 A oscillographic camera at a paper speed of 133.3 inches per minute. The action potential from one of the two nodal fibers was recorded with reversed polarity to facilitate the distinguishing of the two curves.

The heart was allowed to beat spontaneously throughout the experiments. During the initial control period of 30 to 60 minutes, transmembrane potentials were recorded from various portions of the A-V node as identified by action potential configuration and anatomic location in order to accurately map and time normal A-V transmission. The site of microelectrode impalement was observed through a dissecting microscope* at 15X and plotted on a chart with reference to various anatomic landmarks. Subsequently, alterations of A-V conduction were produced by adding isoproterenol (0.25 to 1.0 mg. per liter) or deslanoside C (0.2 to 0.4 mg. per liter) to the perfusate.

Presentation of the data is facilitated by an analytical diagram similar to that used in clinical electrocardiography and by a map of the A-V junctional region. Time values are expressed in milliseconds (msec.). Various type of fibers as identified by location and action potential configuration have been classified according to Paes de Carvalho[14]: AN (atrio-nodal), N (nodal), NH (node His).

Results

A. Concealed A-V nodal re-excitation in the presence of sinus rhythm. Fig. 1 shows an example of re-excitation concealed within the A-V node. Fibers N1 (upright action potential) and N2 (inverted action potential) of this figure were both located close to the bundle of His in the NH region of the node. The atrial intervals were regular. A rather marked delay in conduction (158

*American Optical Co., Buffalo, N. Y.

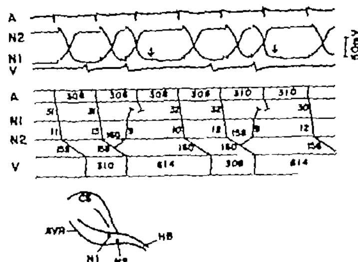


Fig. 1. Concealed re-excitation within the A-V node. *Top tracing:* Atrial electrogram (*A*). *Middle two records:* Transmembrane action potentials from two fibers in the NH region of the A-V node (*N1* and *N2*). Action potential polarity reversed in fiber N2. *Bottom tracing:* Ventricular electrogram (*V*). Small local response follows the third sinus impulse in fiber N1 (*arrow*). Time sequence of re-excitation is shown in the diagram (time in msec.). *Inset at bottom left:* Schematic map of the A-V nodal region. *CS:* Ostium of the coronary sinus. *AVR:* Atrioventricular ring. *HB:* Bundle of His. Discussion in text.

msec.) was seen below the NH region. Following the transmission of two successive impulses, the third atrial beat was not accompanied by ventricular activation, thus producing a ventricular interval double the atrial cycle length. However, in the A-V node premature depolarization of fibers N1 and N2 was demonstrated almost simultaneously with the inscription of the ventricular electrogram. This premature A-V nodal discharge was characterized by (1) reversed time sequence of depolarization in fibers N1 and N2 in contrast to the preceding conducted beats, (2) a slight decrease in the amplitude of the action potentials, and (3) the presence of a small local response in fiber N1 (arrow) probably caused by forward conduction of the next atrial impulse. Although the time difference* between depolarization of fibers N1 and N2 was practically unaltered, fiber N2 was now activated earlier than N1.

The third deflection of the atrial electrogram appeared to be of sinus origin since the morphology and timing were identical to those of previous and subsequent atrial beats. Conduction of this beat was blocked within the A-V node engendering only a *local response in fiber N1*. Hence, re-excitation of the A-V node was concealed. Similar phenomena were repeatedly and regularly noted throughout the long strip from which this figure has been reproduced.

B. Reciprocal activation of the ventricles in the presence of A-V junctional tachycardia. In Fig. 2 ventricular activation preceded depolarization of fiber N (NH region), suggesting that the impulse originated below this fiber. Retrograde conduction to the atria with progressive prolongation of the NH atrial conduction time occurred until a premature discharge of the nodal fiber followed the third atrial beat. This nodal excitation was followed by premature ventricular activation and indicated forward conduction. The starting point of forward conduction was above fiber N (NH region) and in or below the atrial tissue. In this instance initiation of forward conduction did not occur until the NH-atrial conduction time was prolonged beyond 186 msec. This appears to be a classic example of reciprocal beating.

C. Demonstration of multiple functional pathways within the A-V node. The presence of multiple pathways with different properties of conduction and possible

*The term "time difference" rather than conduction time is used [illegible] the sequence of activation of fibers N2 and N1 may not have been caused by the same excitation front.

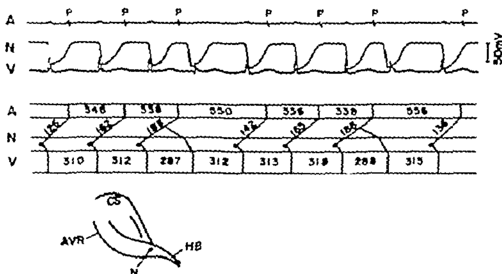


Fig. 2. Reciprocal activation of the ventricles in the presence of A-V junctional tachycardia. Retrograde conduction time between fiber N (NH region) and the atria is successively prolonged until reciprocal, forward conduction to the ventricles occurs, resulting in a longer atrial interval. Reciprocation occurs when N-A conduction time exceeds 186 msec. The ventricular complex of the return beats demonstrates a slightly different contour.

return of an impulse within the A-V node were demonstrated in Figs. 3-6. In this experiment isoproterenol (0.25 mg. per liter) was added to the perfusate after a 1 hour control period. The basic regular mechanism showed a predominantly downward deflection (P) in the atrial electrogram and was assumed to be of sinus origin. On the other hand, premature systoles were accompanied by a polyphasic complex (P") and were engendered by A-V nodal beats. The reason for these distinctions will be discussed later. Thirty minutes after the addition of isoproterenol, re-excitation of some nodal fibers appeared and persisted throughout the experimental period (123 minutes).

Eight of fifteen records taken 30 to 65 minutes after the administration of isoproterenol are shown in Fig. 3. In strips b-f the electrode at B4 (inverted action potentials) remained in the same fiber, whereas a second electrode (upright action potentials) was successively impaled in various nodal fibers (A10, A8, A7, A5, and A2). The sites of electrode impalement in strips a-g and k are also shown in the schematic map of the A-V junctional region (Fig. 3). Activation time of various fibers is determined with reference to the atrial electrogram.

In the presence of sinus (I) beats, activation of nodal fibers mainly in the AN region preceded the atrial electrogram (At). However, fibers located further downstream in the A-V node were sequentially depolarized, suggesting the presence of forward conduction. In strips b-e the electrode A was impaled in the right side of the node and successively closer to the other electrode at B4. In strip k electrode A remained in fiber A5 as in strip e, whereas the electrode B was impaled in B1 distal to B4. The following observations were made on these records: (1) Decremental conduction might be suggested in fibers A8, A7, and A5, as shown by a gradual diminution of the action potential amplitude. (2) A smaller but distinct second peak appeared immediately after the initial depolarization of fiber A5 (strips e and k, beats 1 and 2). An even smaller second peak was seen in fiber A7 (strip d, beats 1 and 2), which was upstream to A5. In addition, the time interval between peaks was greater than in fiber A5. A remnant of the second peak could be seen as a small negative after-potential (arrow) in fibers A10 and A8 (strips b and c). (3) Whenever the action potential of fibers B4 and B1 showed a normal amplitude and upstroke velocity, the impulse was propa-

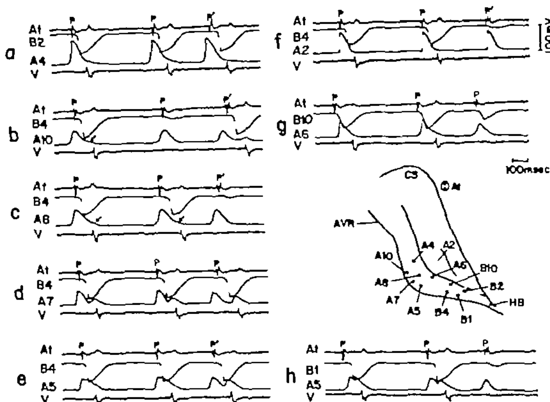


Fig. 3. Multiple functional paths within the A-V node. U, Atrial electrogram. P, Sinus beat. P', A-V nodal beat. One electrode (inverted action potential) was impaled in the same fiber (B4) during recordings b-f. As the second electrode (upright action potential) was moved closer to B4 along the right side of the A-V node, the amplitude and upstroke velocity of the action potential decreased in A8 through A5 (strips c, d, e, h). Conduction to the ventricles occurred only in the presence of a propagated response in fiber B4, and was accompanied by a second action-potential peak in the repolarization phase of fibers A5, A7, A8, and A10. These findings were observed in the presence of sinus beats (beat 1 and 2) as well as nodal beats (beat 3). A second action-potential peak was not seen in fibers (B2, A6, B10) located in the left side of the A-V node (strips f, g). Inset at right shows location of various fibers in the A-V junctional region. See text for detailed discussion.

gated to the ventricles and a second peak appeared in fibers A5 and A7. Contrarily, when only a local response was seen in fiber B4, neither ventricular activation nor the second depolarization in the fibers of the right side of the A-V node was recorded (strip b, beat 2). (4) Initial depolarization of fibers A5, A7, A8, and A10 often caused action potentials with similar amplitude and configuration irrespective of the presence or absence of conduction block to fiber B4 and the ventricles, as seen in strip b, beat 2.

All of these conduction phenomena were even more clearly demonstrated in the presence of nodal (P') beats (see strips b, c, d, e, and h, beat 3). In these instances, conduction between fibers A10 and A5 appeared to be slower than in the presence of sinus (P) beats, and the interval between the two peaks of the action potential was markedly prolonged. The second peak was clearly seen even in fiber A10 (strip b, beat 3).

On the other hand, analysis of other strips (a, f, and g) of this figure revealed the following points. (1) The action potentials from fibers (A6 and B10) in the left side of the A-V node did not show a second peak. (2) Whenever fibers A6 and B10 showed a propagated response, the ventricles were excited. Contrarily, activation of the ventricles always failed when only a graded response occurred in these fibers (A6 and B10). Conduction block to these fibers in the left side of the node was seen more frequently in the presence of nodal (P') beats than in the presence of sinus (P)

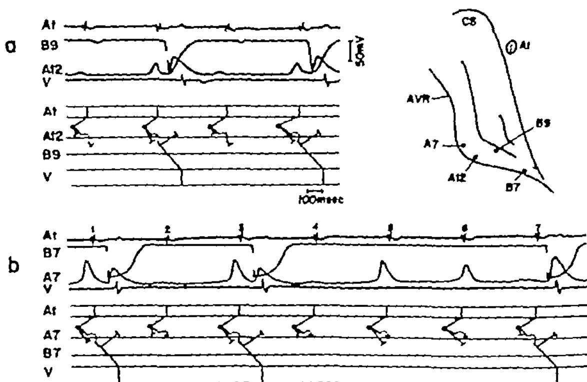


Fig 4 Concealed re-excitation in the right side of the A-V node Inset at top right shows location of various fibers All beats are A-V nodal in origin. Open circles in the diagram indicate estimated time of discharge of the A-V nodal pacemaker Dotted area show bypassing of fiber A7 or A12 by the impulse transmitted through the left side of the node In strip a 2 1 conduction block is seen in fibers A12 and B9 with alternating local responses Ventricular activation always and exclusively follows a propagated response in fiber B9 (left side of the node). This is accompanied by a second and even greater action potential in fiber A12 (right side of the node) *after the initial and incomplete depolarization. In b a higher degree of block is present. The action-*potential amplitude in fiber A7 (right side of the A-V node) produced by initial depolarization, is independent of conduction to the ventricles (cf beats 1 3 5 and 7). Re-excitation of this fiber always follows activation of fiber B7 (bundle of His). Further discussion in text

beats. (3) Atrial fibers (A2) adjacent to the A-V node and on the wall of the coronary sinus were activated later than fibers in the A-V region and followed the atrial electrogram (recorded from the roof of the coronary sinus)

Several of these observations are further illustrated in Fig 4 Exclusively P' type complexes were seen in the atrial electrogram Evidence of nodal origin of these beats is presented in the discussion of Fig 6 In strip *a* 2 1 conduction block was noted in both fibers *A12* and *B9* with alternating *local responses.* Whenever a propagated response appeared in fiber B9 (left side of the A-V node) ventricular activation occurred At the same time a second and even greater action potential followed the initial *and incomplete de-* ... A12 (right side of the node) In strip *b* an advanced second-degree block was seen in *fiber A7* (right side of the A-V node) as well as in fiber B7 (bundle of His) When conduction to fiber B7 and the ventricles occurred (beats 1 and 3) a well-defined second action potential appeared in fiber A7 after depolarization of fiber B7 Furthermore when conduction in the right side of the node produced only a local response in fiber A7 (beat 7) the propagated action potential of fiber B7 was accompanied by a second depolarization of fiber A7 showing the great action potential amplitude Contrarily the action potential amplitude of fiber A7 beat 5 was similar to that in conducted beats 1 and 3 although concomitant activation of fiber B7 and the ventricles did *not occur*

The findings in Figs. 3 and 4 indic

Table I. Statistical analysis of the P-type and P'-type beats

	At-V interval		P P interval	P P' or P' P' interval	P' P interval
	P-type beats	P'-type beats			
Number of measurements	244	116	170	199	73
Mean time	117.2 msec	135.8 msec	588.7 msec.	437.9 msec	736.4 msec
S.D.	±9.30 msec	±8.49 msec	±28.17 msec	±23.70 msec	±30.70 msec
S.D. Per cent of mean	7.93%	6.25	4.79%	5.41%	4.17

S.D., Standard deviation.
At, Atrial; V, Ventricular; P, Atria activated by sinus; P', Atria activated retrogradely by the A-V node.

that (1) fibers in the NH region (B4 and B1) and bundle of His (B7) as well as the ventricles were not activated by the impulse traveling down the right side of the node, but were depolarized by an impulse spreading through the left side of the node (2) the second action-potential peak in fibers A5, A7, A8, A10, and A12 (right side of the node) was clearly dependent upon a propagated response in the region of fiber B4 which initiated retrograde conduction exclusively in the right side of the node and (3) this retrograde conduction was decremental and failed to excite the atria. Thus, unidirectional block can be implied in the right side of the A-V node below fibers A5 and A12.

Obviously, strips *a-k* of Fig. 3 could not be recorded simultaneously. Hence, it might be questioned whether a comparison of the activation times of various fibers would be valid in determining the pathways of forward as well as retrograde conduction. The following statistical analysis of the data is presented to justify such a comparison (Table I).

Fifteen recordings were made during a 35-minute period after the first appearance of nodal re-excitation. A total of 462 beats, 254 sinus (P) and 208 nodal (P') was analyzed. A second-degree forward conduction block accompanied both types. However, nonconduction to the ventricles occurred more frequently with P' beats (92 of 208 beats or 44.2 per cent) than with P beats (10 of 254 beats or 3.9 per cent). The mean value and the standard deviation (S.D.) for the atrioventricular (At-V) intervals in the conducted beats, sinus (P-P) and nodal (P-P' or P'-P') intervals, as well as the compensatory pause (P'-P) are shown in Table I. It may be concluded from these data that (1) the rate of both sinus (102 ± 5 per minute) and nodal (137 ± 7 per minute) mechanisms remained unaltered during this period and that (2) whenever an impulse was transmitted to the ventricles, its conduction through the A-V junctional tissues was constant. Hence, a graphical construction of forward and return pathways within the A-V node by the plotting of the timing of various fibers appears to be valid. One additional observation was that A-V nodal beats showed a longer conduction time and a higher incidence of block.

Based on these data, two summarizing figures (Figs. 5 and 6) are presented. The location and activation time of various fibers in and near the A-V node in the presence of P-type beats is shown in Fig. 5,*a*. Fibers A9, A4, A10, A8, and A7 were depolarized early and almost synchronously. This indicates simultaneous arrival of an impulse at the atrionodal junctional (AN) region, and suggests the sinoatrial origin of these P-type beats. Subsequent conduction through the middle (N) region of the A-V node occurred only in the left side while it was blocked in the right side. Since the timing of the second action-potential peak in fiber A5 (35 msec.) was almost synchronous with the depolarization of fiber B4 (36 msec.), retrograde conduction through the right side of the node must

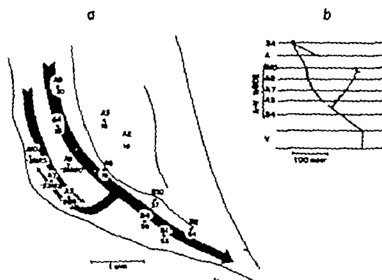


Fig. 5. a, Pathways of re-excitation in the presence of sinus beats. The numbers below individual fiber sites represent the time of activation with reference to the atrial electrogram. The figures in parentheses show the time of the second action-potential peak caused by re-excitation. Tapering of arrows indicates decremental conduction. The At-V interval is 117 msec., as shown at the bottom of the map. b, Diagrammatic representation of re-excitation in fibers located in the right side of the A-V node. Open circle at SA shows estimated time of S-A nodal discharge. Dotted line between fiber A5 and the turning point indicates conduction block.

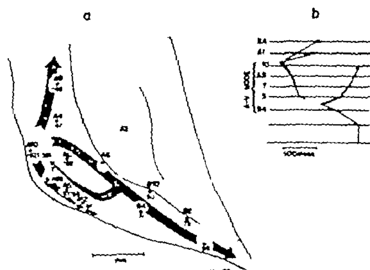


Fig. 6. a, Pathway of re-excitation in the presence of A-V nodal beats. Earliest activation is seen in fiber A10. Sequential activation of fibers A10 to A5 is slower than, but similar to, conduction in the presence of sinus beats (Fig. 5). b, Graphic representation of re-excitation similar to that shown in Fig. 5,b.

have started somewhere between A5 (or A6) and B4 (within a distance of approximately 2 mm.). Furthermore, retrograde conduction caused only a local response of fiber A10 after 68 (123-55) msec. and did not reach the atria. Forward conduction time between B4 and the ventricles was 61 (117-56) msec. Fig. 5,b diagrammatically shows the time sequence of re-excitation in the right side of the A-V node.

On the other hand, the spread of excitation in the A-V node in the presence of

P' type beats is shown in Fig 6,*a* In this instance, the earliest depolarization was recorded in the region of fiber A10 (−82 msec.) This was followed 30 to 35 msec later by the activation of fibers above (A9) to the left (A8) and below (A7) Activation of the atria (At) after the discharge of fiber A10 occurred later (82 msec.) than in the presence of sinus beats (32 msec.) Hence, it is concluded that P' type beats originated in a portion of the A V node near fiber A10 The gradual increase in P' type beats with a similar cycle length and finally the entire replacement of the P type beats suggest a nodal rather than sinus origin of the impulses, as shown in Fig 4 Successful A V transmission via the left side of the A V node and decremental forward as well as return conduction in the right side of the node were similar to those seen in the presence of sinus beats (Fig 5,*a*) Likewise, the point of return was located in the same area as in the sinus beats. Although the time difference between the activation of fibers A10 and B4 was greater with nodal beats, forward conduction time below fiber B4 (64 msec.) did not differ from that of the sinus beats (61 msec) The time sequence of re-excitation in the right side of the node is shown diagrammatically in Fig 6,*b*

Comment

In the present study inhomogeneity of conduction which permitted a slow but successful transmission in one region of the specialized conducting system while decrementing in another allowed the impulse to preferentially travel through the left side of the A V node, turn and be transmitted in a retrograde fashion along the right side of the A V junction where forward conduction was blocked (Figs 3-6) Furthermore in Figs 1 and 2 re-excitation followed in the wake of prolonged A V conduction and occurred in an area of the A V transmission system in which conduction was most severely depressed findings compatible with the concept of re-entry

These arguments are open to criticism if one assumes that re-excitation may be an expression of a properly timed spontaneous pacemaker discharge However evidence against an independent pacemaker is shown in Fig 5 In this instance fiber A5 was initially depolarized in a forward direction at −2 msec and re-excited in a retrograde fashion at 55 msec or simultaneous with fiber B4 (56 msec) The turning point occurred between A5 (or A6) and B4 an anatomic distance of less than 2 mm Hence, any independent pacemaker responsible for retrograde conduction must necessarily be located within this small region. Furthermore demonstration of re excitation of fibers in the right side of the node only in the presence of a propagated response in fibers B4 or B9 implies actual dependence of such pacemaker discharge upon the impulse traveling down the left side of the A V node. It is also obvious that all previously published cases of reciprocal rhythm would be vulnerable to this same criticism

Finally even if one were to assume the formation of a new impulse due to spontaneous pacemaker discharge engendering the second action potential peak, unidirectional block and functional longitudinal dissociation must still be invoked since conduction was not observed for a second time in the left side of the A V node The possibility of spontaneous pacemaker activity appears to be quite remote when precise timing and sequence of activation are studied Furthermore, all observed phenomena can be adequately explained by inhomogeneous conduction alone without implicating independent or dependent formation of a second impulse In view of the foregoing discussion the explanation of Fig 1 by return conduction as illustrated in the diagram appears to be more likely than by an independent pacemaker discharge.

Hence, these studies suggest that under certain experimental conditions, an impulse originating either in the sinus or the A V node may decrement in one portion of the A V junctional tissues while being conducted slowly in another portion turn and re enter the region of decremental conduction and engender concealed or manifest conduction in an opposite direction. Although the simplest and most convincing example of a re-entry mechanism has been shown only *in the A V junctional tissues*, the idea cannot be dismissed that a similar disturbance in a peripheral part of the ramification of the specialized conduction sys-

may cause the same mechanism when unidirectional block and delayed conduction are present.[9]

Finally, these experiments may serve as a model for future studies on re-entry in the A-V node as well as in other regions of the specialized conducting tissues.

Summary

Inhomogeneous conduction in the A-V node as well as concealed and manifest A-V nodal re-excitation were observed in isolated perfused rabbit hearts during the course of electrophysiologic studies on A-V transmission in 98 experiments. Through the use of two simultaneously impaled glass microelectrodes in the A-V junctional tissues, spread of excitation in this region was studied with reference to the atrial and ventricular electrograms. Re-excitation followed in the wake of prolonged A-V conduction and occurred in an area of the A-V transmission system in which conduction was most severely depressed. In some instances, inhomogeneity of conduction permitted a slow but successful transmission in one region of the specialized conducting system with diminution in another. Thus, the impulse was permitted to travel preferentially through the left side of the A-V node, turn and be transmitted in a retrograde fashion along the right side of the A-V junction, where forward conduction was blocked. These results were obtained in the presence of both sinus and A-V junctional beats and appeared to be compatible with the concept of re-entry.

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Case reports

Idiopathic cholesterol pericarditis with effusion

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Pericardial effusion containing crystals of cholesterol was described first by Alexander[1] in 1919. His patient had myxedema and a chronic pericardial effusion which had a "scintillating gold paint appearance" due to the presence of crystals of cholesterol suspended within it. Since then, several additional cases of hypothyroidism with cholesterol pericarditis have been reported.[2-4] Following the institution of appropriate thyroid replacement therapy, marked improvement with resolution of the effusion generally has occurred.

In addition to myxedema, cholesterol pericarditis has been described in patients with several other systemic diseases. These conditions include tuberculosis,[6,7] rheumatic heart disease,[8] myocarditis, and rheumatoid arthritis.[9-11] However, the occurrence of cholesterol pericarditis unrelated to a systemic illness known to involve the heart is rare, and to date only 5 cases of idiopathic cholesterol pericarditis have been reported in the literature.[1-] The following case report illustrates some of the features of this disease state.

Case report

W. L., a 66-year-old businessman, was hospitalized for evaluation of dyspnea and cardiomegaly in May, 1963.

In 1959 a routine chest film had shown cardiac enlargement (Fig. 1). He remained asymptomatic during the next 3 years. Ten months prior to the admission he noted the onset of dyspnea on exertion and mild peripheral edema. A dull precordial discomfort became evident, especially when he was supine. Examination at that time showed marked cardiomegaly, distention of the neck veins, basilar râles, hepatomegaly, and slight tachycardia. Digitalis and diuretic therapy produced temporary improvement, but during the 4 months prior to admission he had progressive dyspnea and anorexia.

There was no past history of cardiopulmonary illness or chest trauma. He had not been exposed to tuberculosis, and a review of previous chest films from 1958 until the present did not show tuberculous changes in the lungs.

On admission the vital signs were: blood pressure 130/90 mm. Hg, pulse 100, respirations 24, and temperature 37°C. A pulsus paradoxus of 12 to 15 mm. Hg was observed. The neck veins were markedly distended, and venous pulsations showed prominent waves and rapid y descent. Retinal veins were engorged. Precordial cardiac pulsations were neither visible nor palpable. The left border of cardiac dullness, as outlined by percussion, extended to the anterior axillary line. Heart sounds were distant and no murmurs were audible. Chest expansion was moderately restricted but the lungs were clear. The liver was enlarged, smooth, and nontender, with the inferior edge palpated 5 cm. below the right costal margin. There was no evidence of ascites. Slight pretibial and pedal edema was noted.

The hematocrit was 50 per cent, white blood cell count was 7,600 per cubic millimeter, and the differential count and blood smear were normal.

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Fasting blood sugar was 170 mg per cent. The blood urea nitrogen, PBI, LDH, and liver function tests were all within normal limits. Total serum protein was 7.0 Gm. per cent with 4.0 Gm. of albumin and 3.0 Gm. of globulin. Serum electrolytes were normal with the exception of an initial carbon-dioxide combining power of 39 mEq. per liter which returned to normal after therapy. The tuberculin



Fig. 1. Roentgenogram of the chest taken in 1959. There was minimal enlargement of the cardiac silhouette due either to pericardial effusion or to cardiomegaly.

skin test was positive, but the histoplasmin, coccidioidin, and blastomycin skin tests were all negative. An antinuclear factor test was negative.

The electrocardiogram showed diffuse low voltage of the QRS complex and flattening of the T waves. A chest film on admission is shown in Fig. 2A.

On the third hospital day, 1,450 ml. of greenish-gold pericardial fluid in which was suspended white particulate matter was removed from the pericardial space. Fig. 2B shows the air-filled pericardial sac and the cardiac silhouette. Microscopic examination of the pericardial fluid demonstrated sheets of flat colorless cholesterol crystals, as shown in Fig. 3. There were also large round cells filled with globules of sudanophilic material, part of which was strongly birefringent under polarized light (Fig. 4). Cultures of this fluid yielded no growth for routine bacterial organisms and for *Mycobacterium tuberculosis*.

After this pericardiocentesis there was considerable improvement in dyspnea, a decrease in venous pressure, and an increase in voltage of the QRS complex and T wave in the electrocardiogram. However, the patient rapidly developed fever, pericardial friction rub, chest pain, weakness, and lethargy. A large left pleural effusion was noted and repeated thoracenteses were performed. The pleural fluid had the same gross and microscopic characteristics as that initially removed from the pericardial cavity. A subsequent pericardial aspiration revealed clear serosanguinous fluid which did not contain crystalline material on microscopic examination. Fever abated by the seventh hospital day, and his clinical status improved sufficiently to permit his discharge 15 days after admission. Table I presents the data of the lipid and protein analysis of the patient's serum and pericardial fluid.

One month later he was readmitted for evaluation

Table I. Lipid and protein contents of patient's serum and pericardial fluid

	Serum	Pericardial fluid	
		First aspiration	*Second aspiration*
Lipid (mg. %)			
Total lipid	704	192	235
Cholesterol ester	229	52	74.4
as cholesterol	149	36	38.2
Free cholesterol	38	75	9
Triglyceride	129	18	43.8
Lipid phosphatase	9.7	1.4	2.8
Proteins (Gm. %)			
Total	7.0	6.7	
Albumin	4.0	4.5	
Globulin			
Alpha 1	0.37	0.30	
Alpha 2	0.50	0.20	
Beta	1.00	0.70	
Gamma	1.13	1.0	



Fig. 2 A Roentgenogram of chest taken on admission. The appearance of the cardiac shadow was consistent with massive pericardial effusion.
Fig. 2B Chest film taken after initial pericardial aspiration and injection of air into the pericardial cavity. Note the relatively normal size of the heart.

He was completely asymptomatic, and had not taken any cardiac medications. The cardiac size was normal, and the heart sounds were of good quality. At the time of this writing, 16 months after the initial diagnosis, he is clinically well and has a normal cardiac configuration on the chest x-ray film.

Review of clinical features

As stated previously, only 5 cases of cholesterol pericarditis from the literature as well as the present one may be considered to be idiopathic. The clinical features of these 5 cases are described below in greater detail, and the salient points are summarized in Table II. At the time when pericardial effusion was diagnosed these 5 patients varied in age from 17 to 45 years. There were 3 men and 2 women. The common presenting symptoms were dyspnea, fatigue, and substernal distress. These were frequently mild and not incapacitating. In one instance there were no presenting complaints, and the diagnosis was established after evaluation of cardiomegaly found on a routine chest



Fig. 3. Sheets of flat, colorless "cholesterol" crystals in pericardial fluid demonstrated under microscope.



Fig. 4. Microscopic demonstration of large round cells filled with globules of sudanophilic material in pericardial fluid obtained from the first aspiration.

Table II. Salient features of the 5 reported cases of idiopathic cholesterol pericarditis

Author	Age Sex	Duration of symptoms	Cholesterol (mg%)	Pericardial fluid: Cholesterol (mg%)	Pericardial fluid: Protein (Gm%)	Therapy	Course
Ada	27 F	2 mo.	167	120	5.7	Surgical exploration of pericardial sac with removal of fluid	Recovery
Aitken	45 F	3 y	333 / 200	—	—	Multiple aspirations of fluid antituberculous drugs	Recovery
Genecin	37 M	None	190 / 243	162	6.1	Multiple aspirations pericardiectomy	Recovery
Hanking	45 M	14 y	—	140	—	Multiple aspirations pericardiectomy	Recovery
Crow	41 M	8 yr	162	—	6.9	Aspiration pericardial biopsy	Recovery

x-ray film.[11] The signs were uniformly those of massive pericardial effusion with elevated venous pressure and in 3 cases hepatomegaly. Ascites and peripheral edema were present in 1 patient. In 4 cases an electrocardiogram was obtained and in each the main finding was low voltage of the QRS complex. Roentgenograms of the chest invariably demonstrated massive enlargement of the cardiac silhouette generally with clear lung fields. Laboratory data showed no consistent abnormality in blood count, sedimentation rate, serum proteins, and other blood biochemical constituents. Determinations of serum cholesterol were reported in 4 cases and in each instance the cholesterol level was found to be within normal limits. In 2

patients the concentration of cholesterol in the pericardial fluid was slightly less than that in the serum.

The characteristics of the pericardial fluid were similar. The color of the fluid varied from gold to brown, and had an opalescent and shimmering quality due to the suspension of golden or white particulate crystals. The protein content was high in the 3 cases in which this value was determined; the range was from 5.7 to 6.9 Gm. per cent. Cell counts were low and showed a predominance of mononuclear cells.

Tissues were available for pathologic study in 4 cases. The pericardium was thickened, fibrotic, and infiltrated with small numbers of nonspecific mononuclear cells. Cholesterol clefts were noted in each case, and foreign-body giant cells were present in 2 cases.

In 3 of the 5 reported cases and in the present case, removal of pericardial fluid by aspiration alone resulted in complete recovery.[13-17] In the other 2 cases, pericardiectomy was performed after repeated pericardiocenteses, and recovery was complete in both.[1,14] Follow-up periods ranged from 1 to 8 years. All 5 patients were in apparent good health and had not experienced an exacerbation of pericarditis.

Discussion

Pericardial effusions containing crystals of cholesterol are rare, and have usually been associated with systemic diseases well known to cause chronic indolent pericarditis. The etiology of the cholesterol pericarditis in our case is obscure. There was no evidence of a primary systemic disease nor was there any history of antecedent chest trauma or pericardial disease. We have no satisfactory explanation for the cardiomegaly demonstrated in the chest x-ray film taken in 1959. At that time he might have had a small amount of fluid in the pericardial cavity. No information in regard to his cardiac status was available in the ensuing 3 years, although he was asymptomatic. It is probable that the accumulation of the pericardial fluid had been slowly progressive. Ten months prior to his hospitalization, significant hemodynamic changes must have occurred to produce manifestations of both left and right "restrictive" ventricular failure.

After the initial pericardiocentesis, there was striking improvement in the patient's clinical status. The heart size was either normal or minimally enlarged, as demonstrated in the air-filled pericardial sac. There was no positive cardiac finding to suggest the presence of congenital or valvular heart disease. The acute episode of fever and chest pain after the pericardiocentesis was most likely due to the entrance of pericardial fluid into the pleural cavity through the puncture made by the aspirating needle, followed by production of an acute "sterile" pleurisy.

We believe that in a patient with long-standing pericardial effusion the possibility of cholesterol pericarditis with effusion, either idiopathic or associated with other systemic diseases, should be seriously considered. We do not have an adequate explanation for the mechanism and production of cholesterol pericarditis. It is possible that unnoticed pericardial trauma or infection of even mild degree may predispose to the entrance into the pericardial cavity of soluble lipoproteins. If lipoprotein resorption from pericardial fluid were retarded, breakdown of these elements might occur, with the liberation of water-insoluble lipids. When these free lipids reached a certain concentration, aggregation to form a crystalline structure such as cholesterol might occur. This is exemplified in our case by the excessive amount of free cholesterol in the pericardial fluid obtained from the first aspiration. The presence of cholesterol in various body spaces is known to be irritating to the surrounding tissues.[17] In this instance, the presence of cholesterol-containing crystals in the pericardial cavity would, through constant irritation, promote a chronic pericardial effusion. This hypothesis fits well with the observation in this and 3 other cases that removal of the cholesterol crystals by means of simple aspiration brought about complete resolution of the effusion. Since the factors which led to the initial pericardial inflammatory process and effusion were presumably no longer present, removal of the source of chronic irritation resulted in full recovery.

Summary

This report describes the presence of massive pericardial effusion in a 68-year-old man who was markedly disabled and presented manifestations of restrictive ventricular failure. Initial pericardiocentesis yielded greenish-gold pericardial fluid which contained excessive amounts of free cholesterol and many cholesterol crystals. Removal of the pericardial fluid by two separate aspirations resulted in the disappearance of all the symptoms and signs. No definitive etiological factor was found, and the case was considered to be one of idiopathic cholesterol pericarditis with effusion.

In the literature only 5 cases of similar nature were reported. The salient clinical features of these 5 cases were reviewed and summarized. Complete recovery resulted from multiple pericardiocenteses alone in 3 cases, whereas subsequent pericardiectomy was required in the other 2 cases.

We wish to express our thanks and appreciation to Dr. William N. R. Nye for the biochemical analysis of the patient's serum and pericardial fluid. We are indebted to Dr. Roger Terry for the pathologic examination of the pericardial fluid. The secretarial assistance of Mrs. Bonnie Sollie is gratefully acknowledged.

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Double-outlet right ventricle: intact ventricular septum, mitral stenosis, and blind left ventricle

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Origin of both great vessels from the right ventricle (double-outlet right ventricle) has been the subject of a number of reports and reviews during the past few years.[1-4] In this malformation a ventricular septal defect serves as the only outlet for the left ventricle. In the absence of pulmonary stenosis the symptomatology and physical findings are those of a large ventricular septal defect. When pulmonary stenosis is present, the clinical manifestations are quite similar to those of the tetralogy of Fallot, with the exception of electrocardiographic abnormalities described recently by Mirowski and associates.[5] It is the purpose of this report to describe the clinical course, physical findings, and postmortem observations in a child who had a double-outlet right ventricle without pulmonary stenosis, associated with the additional intracardiac malformations of severe mitral stenosis and an underdeveloped left ventricle. The ventricular septum was intact. Pulmonary venous return gained access to the right heart through a small ostium secundum atrial septal defect. A striking physical finding was a continuous murmur near the upper right sternal margin.

Case report

The patient was born at term after an uneventful gestation to a 33-year-old woman, gravida II. His birth weight was 6 pounds and 14 ounces. No abnormalities were noted in the immediate neonatal period.

During the first 6 weeks of life his gain in weight was poor, and occasionally his respiratory rate seemed to be rapid. Cyanosis and congestive heart failure appeared during the sixth week of life. A continuous murmur to the right of the upper sternum was heard at this time. His clinical response to digitalization was rapid and signs of cardiac decompensation disappeared within 48 hours, although cyanosis persisted.

Thereafter growth was steady but below average. The intensity of his cyanosis did not change. When the child was approximately 2 years of age, his parents noted that his exercise tolerance was decreasing and even mild activity was associated with rather severe exertional dyspnea. He was admitted to the Frank T. Tobey Memorial Children's Hospital for diagnostic studies.

The patient was a small and thin 2-year-old white male who weighed 20½ pounds and had a height of 31 inches. He was dyspneic at rest. The lips and nailbeds were moderately cyanotic, and there was moderate clubbing of the digits. The pulse rate was 100 and regular, and his respiratory rate was 50 per minute. Blood pressures in the right arm and right leg were 130/50 and 140/50 mm. Hg, respectively. Prominence of the left side of the chest was noted and there was a very forceful right ventricular parasternal systolic thrust. At the upper right sternal margin and in the suprasternal notch there was a systolic thrill which ac-

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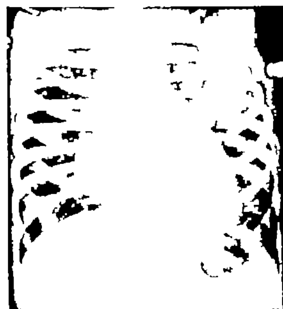


Fig 1 Posteroanterior chest roentgenogram. The heart is only slightly enlarged There is a narrow cardiac waist, straight left border heavy vascular markings the hilar region and clear peripheral lung fields. The heart ppears to be "egg shaped.

companied the systolic component of a continuous murmur of medium pitch and moderate intensity (Grade 3/6). The second heart sound was single and loud. The peripheral pulses were full and bounding reflecting the wide pulse pressure.

The chest roentgenogram demonstrated moderate cardiac enlargement, with prominence of the right atrial curve and pulmonary artery segment a narrow cardiac waist and an increase in the hilar lung markings. The peripheral one third of the lung fields appeared to be devoid of vascular markings (Fig 1).

The electrocardiogram (Fig 2) was unusual. I the standard and unipolar limb leads, separation of the P from the preceding T wave was difficult because of tachycardia. Â QRS in the frontal plane was normal and the "electrical position" of the heart was vertical. The QRS in Lead V was characterized by a QS deflection of small amplitude. QRS deflections in Leads V and V were of small amplitude the configuration was that of an R wave with marked slurring of the upstroke. The T waves were flat in the limb leads and isoelectric in Lead V S-T segment elevation was apparent in Leads V through V.

During cardiac catheterization the right ventricular pressure measured 115/0-5 mm. Hg pulmonary arterial and central aortic pressures were equal 115/50 mm. Hg. Arterial oxygen saturation was 82 per cent The anatomic nature of the lesion

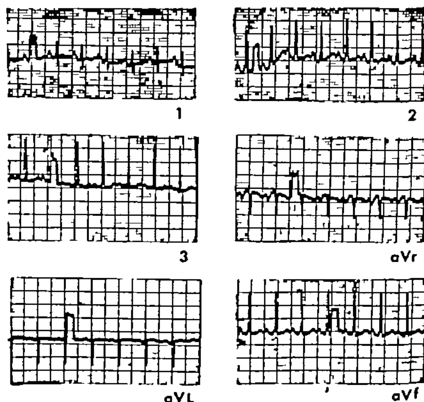


Fig 2 The electrocardiogram *(see also opposite page)* See text for description

was clarified by selective cineangiocardiography Three injections of 9 c c each of diatrizoate methyl glucamine (Renovist) into the right ventricle demonstrated two separate outflow tracts. The ascending aorta and its outflow tract were to the right of the pulmonary artery and its outflow tract In the lateral projection the great vessels were superimposed. The aortic and pulmonary valves were approximately at the same level in the coronal and cross-sectional body planes. The aorta was considerably smaller than the pulmonary artery The pulmonary veins entered the left atrium and a left to-right shunt occurred across a small secundum atrial septal defect. The left ventricle did not opacify and was assumed to be atretic.

An injection of contrast medium into the main pulmonary artery was followed by a brief period of apnea and the patient became very cyanotic The procedure was terminated oxygen was administered and intravenous fluids were started Cyanosis progressively increased, his state of consciousness diminished, and during the last 3 hours of life he had almost continuous generalized seizure activity that was controlled for brief periods only by the administration of intravenous paraldehyde Death occurred 21 hours after the study

Pertinent postmortem findings were limited to the heart and great vessels. Permission to examine the central nervous system was not granted. The heart weighed 95 grams (expected weight 56 grams). Both great vessels arose from the right ventricle and their origins were separated by a prominent muscular bundle. The diameter of the aortic valve measured 5.5 cm. that of the pulmonary artery 4 5

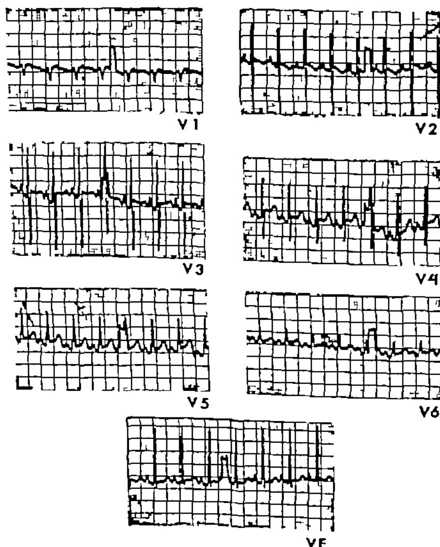


Fig 2 —Cont'd Electrocardiogram.

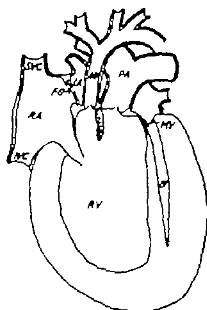


Fig. 3. Diagrammatic representation of the patient's cardiac malformation. There is a small atrial septal defect in the region of the foramen ovale. *The right ventricular cavity is large. The aorta* arises anterior to and to the right of the pulmonary artery and is smaller than the latter structure. The outflow tract of these two great vessels are separated by a small mass of muscular tissue. The mitral valve is extremely hypoplastic and the mitral valve opening is very small. The left ventricle is a band slit-like structure which appears to be buried in the thickened right ventricular wall. *SVC* Superior vena cava. *IVC* Inferior vena cava. *RA* Right atrium. *FO* Foramen ovale. *RV* Right ventricle. *Ao* Aorta. *PA* Pulmonary artery. *MV* Mitral valve. *LV* Left ventricle. *LA* Left atrium.

cm. These valve measurements do not reflect the relative sizes of the two great vessels as observed in the cineangiograms during life (*vide supra*). When the heart was viewed from the lateral aspect the great vessels were superimposed. In the frontal view the aorta arose anterior to and to the right of the pulmonary artery, the latter was considerably larger than the aorta. *Both coronary arteries* arose from the aorta; the anterior descending branch was small and traversed the interventricular sulcus which was displaced far to the left. Both venae cavae entered the right atrium and pulmonary venous return was to the left atrium. There was a small ostium secundum atrial septal defect or a stretched foramen ovale (5 by 6 mm.). The mitral valve measured less than 10 mm. in its greatest diameter and the leaflets were thickened and malformed. The tricuspid valve measured 8 cm. in diameter. The right ventricular wall was thickened and hypertrophied and was separated by an intact septum from the hypoplastic and blind left ventricle (Fig. 3).

Microscopic sections of the lungs showed scattered groups of alveoli filled with pink-staining acellular material. There was generalized thickening of the alveolar septa which appeared to consist of fibrous tissue and metaplastic alveolar lining cells. The fibrous adventitia of the pulmonary arteries was thickened greatly. There was slight thickening of the muscular media of the small pulmonary arteries and arterioles; these vessels contained scattered foci of eccentric intimal thickenings. Elastic tissue staining of these vessels demonstrated very prominent internal and external elastic lamellae.

Discussion

Several congenital malformations of the heart and great vessels may be associated with the physical finding of a continuous murmur: patent ductus arteriosus, severe peripheral pulmonary arterial stenoses, coronary arteriovenous fistulae, ruptured sinus of Valsalva aneurysm, anomalous pulmonary venous connection, pulmonary arteriovenous fistulae, aorticopulmonary fenestration, truncus arteriosus, hemitruncus, and pulmonary atresia with extensive bronchial collateral pulmonary blood flow. None of these conditions was found at autopsy. Ross and co-workers[4] recently described a continuous murmur in 5 patients with defects in the atrial septum and elevated left atrial pressure due to obstructive mitral valve disease. In this situation there is a sustained left atrial-right atrial pressure gradient throughout the cardiac cycle which permits continuous left-to-right shunting of blood across the defect. The site of origin of the continuous murmur has been confirmed by intracardiac phonocardiography. In retrospect it seems to be equally plausible that the continuous murmur heard in this patient was of similar origin.

Double-outlet right ventricle has been *considered to be one of the transposition* complexes. Spitzer designated this anomaly as a Type 2 transposition or "*simple transposition of the aorta*."[7] Grant recently advanced the following attractive theory concerning the embryogenesis of transpositions of the great vessels. *Transposition of the great vessels results from a shift in* the orientation of the fibroplastic continuum lining the primitive cardiac tube that extends from the atrioventricular canal to the truncus arteriosus. As applied specifically to the anomaly *of double-*

outlet right ventricle this fibroplastic continuum is interrupted by abnormal differential growth so that the atrioventricular canal is no longer in continuity with the truncus arteriosus. Since the truncus is no longer fixed to the mitral ring the left ventricle acquires no outlet and the right ventricle will acquire two when the spiral septum divides the truncus. The essential requirement of transposition of the great vessels suggested by Grant's theory fibroplastic continuity of mitral and pulmonary valvular tissue is illustrated well by this patient's anatomic abnormality.

This complicated cardiac malformation was not only a double-outlet right ventricle, but also a variant of the hypoplastic left heart syndrome i.e. severe congenital mitral stenosis and an underdeveloped and nonfunctioning left ventricle. This combination of anomalies may have resulted from the abnormal differential growth suggested by Grant, in association with rudimentary development of the left ventricular sinus portion of the primitive cardiac tube.[8]

Although pulmonary arterial blood was delivered to the lungs under systemic pressure, and there was also obstruction to pulmonary venous return caused by the small size of the defect in the atrial septum histologic changes in the pulmonary vasculature characteristic of pulmonary obstructive disease were not remarkable. Indeed as suggested by the cineangiograms pulmonary flow may still have been in excess of systemic flow.

Summary

The clinical course physical findings, and postmortem observations have been described in a child with double-outlet right ventricle complicated by congenital mitral stenosis and a hypoplastic and nonfunctioning left ventricle with an intact ventricular septum. A continuous murmur was considered to be due to the continuous flow of blood across a small foramen secundum atrial septal defect.

Addendum

Since this paper was submitted for publication, a similar case has been described by MacMahan and Lipa.[10] Although this patient also had an interatrial septal defect a continuous murmur was not described by these authors.

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Clinical pathologic conference

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Clinical abstract

History. It was the first admission for this 25-year-old Negro housewife, mother of 3 children, who came to the Emergency Room because of severe breathlessness that had been present for 2 days. She had apparently been in good health until about 10 months previous when she had had a "flu"-like illness consisting of a sore throat, vomiting, and diarrhea. These symptoms lasted about a week. Shortly thereafter she began to complain of progressive weakness, anorexia, loss of weight (total of 35 pounds), increasing shortness of breath, orthopnea, and ankle edema in the afternoon. The symptoms progressed and 1 month prior to admission she no longer could do any housework. In addition she experienced paroxysmal nocturnal dyspnea. She complained of nausea and vomiting. There were no chest pains, hemoptysis, or cyanosis and except for some epigastric soreness, no gastrointestinal symptoms. About 3 weeks prior to admission, she was admitted to another hospital for 3 days, where she received digitalis and aminophylline. She felt improved for several days. However, the symptoms returned together with more vomiting and "spots before her eyes." She was told to stop the digitalis. As to her past history, she had been told that she had an enlarged heart when she was 5 years of age. However, she could not recall having had rheumatic fever, scarlet fever, or chorea, nor was she told that she had any cardiac murmurs. She had had hypertension and ankle edema during the eighth month of her second pregnancy. Her oldest child had died at 13 months of age with congenital heart disease of unknown type. The patient's sister had had rheumatic fever without any apparent cardiac sequelae.

Physical examination on admission revealed a thin woman in moderately severe respiratory distress. She was 5 feet 5.5 inches tall and weighed 115 pounds. The blood pressure was 94/66 mm. Hg. The pulse was 104 and regular. Respirations were 30 per minute and labored. Her temperature was 101.2°F. Examination of her eyes, ears, nose, and throat revealed nothing remarkable. She had an upper dental plate. The lower molars were in poor repair. The neck veins were not distended. An "a" wave was recorded. One examiner felt a diffusely enlarged thyroid. The breasts were normal. The patient was using the accessory muscles of respiration. Breath sounds were diminished at the bases of the lungs, and there was dullness to percussion at the base of the right lung. No râles could be heard. There was no clubbing, cyanosis, or edema. All peripheral pulses were palpable. There was a slight precordial bulge on the left side. The point of maximum impulse was diffuse and 11 cm. from the mid-sternal line in the sixth left intercostal space. An apical systolic thrill was felt. Both heart sounds were very loud. S_1 was loudest at the apex and at the left sternal border. S_2 was widely split but varied normally with respiration. A sound heard along the left sternal border was called an opening snap by one examiner and S_3 by another. A Grade 3/6, harsh, low-pitched systolic murmur was heard loudest at the apex and radiated into the axilla to the posterior axillary line. A Grade 1-2/6, soft, blowing systolic murmur was heard only at the fifth intercostal space parasternally without radiation. There were no diastolic murmurs. The abdomen was soft. Many striae gravidarum were present. Slight tenderness was noted in the epigastrium and along the left costal margin. The liver was down below the costal margin 11 cm., the spleen, 4 cm. Both were firm and tender. A hepatojugular reflux was elicited. Skin turgor was good. The extremities and neurological examination were normal. There was a fine tremor of the outstretched hands. There was no significant lymphadenopathy. Pelvic and rectal examinations were not performed. Arm-to-tongue Decholin circulation time was 29 seconds. Venous pressure was not recorded. The hemoglobin was 13.9 Gm. The hematocrit was 43 per cent. The white blood cell count was 4,200 with 1 per cent stab cells, 47 per cent neutrophils, 24 per cent lymphocytes, and 28 per cent monocytes. Reticulocytes were 2.9 per cent. Platelets were

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Fig. 1. X-ray film of chest. Heart shadow is enlarged. Bronchial and vascular markings are accentuated. There are no apparent pulmonary parenchymal infiltrates.



Fig. 2. Electrocardiogram. Rate 100, sinus rhythm, axis +150 degrees. P-R interval 0.16 sec. QRS 0.10 sec. P waves notched. There is low voltage in the frontal leads. There is clockwise rotation in the horizontal plane.

numerous. The mean corpuscular hemoglobin concentration was 32. The erythrocyte sedimentation rate was 34. The antistreptolysin-O titer was 12. The protein-bound iodine was 6.4 micrograms. Urinalysis revealed a specific gravity of 1.008, pH 6.0 with no albumin, sugar, acetone, bile, or urobilinogen. There were 2 to 3 red blood cells, 5 to 6 white blood cells, 6 to 8 granular casts, and 3+ bacteria. A chest x-ray film with barium swallow was obtained (Fig. 1). The electrocardiogram (Fig. 2) revealed the following: rate 100, sinus, P-R 0.16 sec., QRS 0.12 sec., mean QRS vector indeterminate, mean T vector −30 degrees, bizarre QRS in limb leads, rsr' in Leads II, III, and aVF, low voltage in limb leads, P biphasic in Leads V_1-V_3, relatively tall R in Leads V_1-V_3. The electrocardiogram was interpreted as being suggestive of right ventricular and left atrial hypertrophy.

Initial treatment consisted of redigitalization, diuretics, and sedatives. There was some clinical improvement. However, about 36 hours after admission, the patient developed ventricular fibrillation. Defibrillation was carried out, and some cardiac activity returned, consisting of low QRS voltage, first-degree and second-degree A-V block, with progressive prolongation of the P-R interval. About 1 hour later all cardiac activity ceased.

Discussion

DR. GUNNAR: This is the story of a 25-year-old Negro woman who was hospitalized because of severe breathlessness. She had been told that at the age of 5 years she had an enlarged heart, but she denied any history of murmurs, rheumatic fever, scarlet fever, or chorea. She was apparently in good health until 10 months prior to her admission to hospital when she had a "flu-like" illness with sore throat, vomiting, and diarrhea that lasted for about 1 week. Shortly after this she began to complain of two groups of symptoms: one was related to a systemic illness, viz., progressive weakness, anorexia, and loss of weight of 35 pounds; the other was related to congestive heart failure, viz., increasing shortness of breath, orthopnea, and ankle edema. Evidently the symptoms progressed gradually, and by 1 month prior to admission she was unable to do any of her housework because of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and some nausea and vomiting. She had no chest pain, hemoptysis, or cyanosis. Except for some epigastric soreness, which was probably related to her cardiac failure, she had no other gastrointestinal symptoms. Three weeks prior to admission she was placed in another hospital for 5 days and was given digitalis and aminophylline, with some improvement. Shortly after discharge the symptoms of

dyspnea recurred associated with more vomiting and spots before her eyes. She was told to stop her digitalis at this time, although the spots before her eyes could have been related either to an excess of digitalis or to low cardiac output.

In her past history this patient had had some hypertension and ankle edema during the eighth month of her second pregnancy. We are told that the oldest child died of congenital heart disease of unknown type but we are not told the age of the youngest child. The patient's sister had had rheumatic fever without any sequelae. Although we cannot decide whether there is a genetic predisposition or an environmental predisposition to rheumatic fever, there certainly is an increased familial incidence.

The physical examination revealed a thin woman in moderately severe respiratory distress. The blood pressure was 94/66 mm. Hg, the pulse was 104 and regular, and the temperature was 101.2°F. The patient had poor teeth. The neck veins were not distended, which seems to me to be a little unusual for a patient in this much distress. The "a" wave recorded in the neck would indicate that there was difficulty in emptying of the right atrium. This would be due either to a loss of compliance of the right ventricle, indicating hypertrophy or fibrosis, or to stenosis of the tricuspid valve. The "a" waves of tricuspid stenosis may be rather distinct flicking types of waves, but in the absence of this sign do not differ from the "a" waves seen in right heart failure. One examiner felt a diffusely enlarged thyroid. However, nothing else in the findings would be consistent with thyrotoxicosis. There was dullness to percussion in the base of the right lung, suggesting pleural effusion. No râles were heard, indicating that there was probably a good deal of interstitial edema which would account for the loss of compliance of the lungs and dyspnea without a great deal of alveolar and bronchiolar fluid. No clubbing, cyanosis, or edema were described at this time. The peripheral pulses were full and, I assume, equal. There was a slight precordial bulge on the left side which when slight is best omitted from the differential diagnosis. The point of maximum impulse was described as diffuse and 11 cm. from the midsternal line in the sixth left intercostal space. This tells me where it is, but not what it is. From the description I do not know whether this is left ventricle or right ventricle. The fact that it is described as diffuse would suggest that it was indeed right ventricle, as would the fact that it was only 11 cm. from the mid-sternal line. However, the fact that it was displaced to the sixth intercostal space would indicate that it was left ventricle. That raises the possibility that it could be both ventricles. When the left ventricle is enlarged, the impulse usually carries the right ventricle and left lower sternal border in during systole. When the right ventricle is enlarged one sees a lift at the left lower sternal border. When both ventricles are enlarged one can frequently see a combination of the apical lift from the left ventricle, just inside this an area of systolic retraction representing the interventricular septum, and then a heave at the left lower sternal border. Without being able to distinguish these two impulses, one can never be sure that there is truly combined ventricular hypertrophy in the face of a heave at the left lower sternal border. The other description which is lacking is whether the impulse was active or quiet. An active impulse would indicate that we are dealing with a volume-overloaded heart, whereas a quiet heart would indicate pressure overload or pericardial disease. An apical systolic thrill was felt. This would indicate in all probability that there was some A-V valvular insufficiency, and if it is assumed that the apex was that of the left ventricle, this would indicate that we are dealing with mitral insufficiency. I have on a few occasions seen thrills at the apex in the presence of severe aortic stenosis, and in the absence of significant mitral insufficiency. However, this usually is in the older individual with a moderate amount of emphysema, which will obscure the associated basal thrill. Both heart sounds were described as being very loud. I assume that S_1 and S_2 were meant. The first sound was loud at the apex and along the left sternal border. The loud first tone at the apex suggests that the mitral valve was not severely destroyed and that either the force of contraction of the left ventricle was increased or some fibrotic process or gradient held the mitral valve open, allowing a larger excursion of the

valve during the onset of ventricular contraction. The second sound was widely split. Here again we have some difficulty. A widely split second sound can be either a widely split sound indicating aortic and pulmonary closure, a closely split second sound followed by an opening snap, or a closely split second sound followed by a third sound. Indeed early descriptions of mitral stenosis included a widely split second sound as one of the characteristics. We are given some more information in the finding that the interval between these sounds varied normally with respiration. If this is true we are probably dealing with a widely split second sound, pulmonary closure being delayed or aortic closure occurring early, and the fact that it moves normally with respiration would tend to make less likely the possibility that we are dealing with such conditions as an atrial septal defect or a complete right bundle branch block. If this were an opening snap and variation were actually noted with respiration the tendency would be for the opening snap to move closer with inspiration, much like paradoxical splitting of the second sound. We should also note other features, for example, the wide transmission of the second component to areas such as the suprasternal notch and the apex of the left ventricle. We are now told about another sound which is a third sound or an opening snap heard along the left sternal border. If this were a third sound the location would suggest that it came from the right ventricle. A Grade 3/6 harsh, low-pitched systolic murmur is described at the apex, radiating into the axilla and to the posterior axillary line. This, again, indicates that our concern is with a patient who has mitral insufficiency. A Grade 1-2/6 soft, blowing systolic murmur was heard only at the fifth intercostal space parasternally and did not radiate. No change in intensity was noted with respiration, but I should still think that this represents a minimal amount of tricuspid insufficiency. No diastolic murmurs were described. *It is a little* difficult to make a diagnosis of a significant shunt or a significant valvular lesion without a diastolic murmur unless I were to make a diagnosis of semilunar valvular stenosis, either aortic or pulmonic. However, none of the systolic murmurs described is suggestive of these diagnoses. When dealing with a tricuspid or mitral regurgitation of significant degree, one would expect that as the large volume of blood returns to the ventricle after being regurgitated into the atrium along with the amount of blood which has to be admitted to make up the forward output, a short diastolic rumble should be heard around the time of the third heart tone. This was not described. If there were a severe left-to-right shunt in either atrial or ventricular septal defect or patent ductus, one would expect a short diastolic rumble after the third heart tone. We are not likely to be dealing with a right-to-left shunt since the patient was not cyanotic, so that I must make some assumptions about murmurs if I am to regard this patient as having a valvular defect or a shunt. The rest of the examination revealed that the patient was in right heart failure with the liver down 11 cm. below the costal margin and the spleen 4 cm. Splenomegaly in the face of a short history of congestive heart failure is extremely rare. Hepatojugular reflux was elicited and the patient had a prolonged circulation time with Decholin confirming right heart failure.

If this patient does not have a lesion of the nature of a shunt or a valvular defect we must assume that we are dealing with a primary myocardial lesion. This could fit the clinical picture. One would have to say that the diagnosis of an enlarged heart in this patient at the age of 5 years had been made even though there was difficulty in knowing what the normal size of the heart was in a 5-year-old. This difficulty was well-recognized 20 years ago. She was then in good health until she developed a flu-like illness. This could have represented infection by a number of viruses which are associated with myocardial disease such as that which causes psittacosis, adenovirus, herpes, and Coxsackie. In all probability many others will be found when better techniques are developed for recognizing viral infection and myocardial involvement. As you may know, the only viruses that have been isolated from the heart have been those of the Coxsackie group. This has been well documented in children, in patients with pericardial effusion, and on two occasions in patients with myocardial biopsies performed during their acute illness. We

could assume that this was the onset of her illness. She developed myocardial disease which progressed relentlessly with increasing fibrosis and increasing destruction of muscle. The heart dilated. We would assume that this dilatation produced what we have always in the past called relative mitral and tricuspid insufficiency. This more likely represents an inability of the papillary muscles to accommodate for their displacement by the dilating ventricle making the valve truly and severely insufficient. We then could explain the failure with murmurs and with extra heart tones, such as the third tone. In all probability, if this were the illness involved, the patient would terminally have had pulmonary embolism since these patients frequently have endocardial mural thrombi.

Could this be postpartum heart disease? We are not told when her last pregnancy was. In any instance, we really do not know what postpartum heart disease is. The likelihood is that it represents a group of diseases, including nutritional disorders, viral diseases, and some relative of toxemia of pregnancy. The onset of symptoms is usually within 3 months of delivery; symptoms that begin more than 6 months after the last delivery are unacceptable for a diagnosis.

Aside from viruses there are other infectious and noninfectious agents which can involve the myocardium. The list is long. However, one would be remiss if he did not mention coronary artery disease. Occasionally at autopsy we see a young Negro female who has myocardial infarction.

The difficulties which I have with the diagnosis of primary myocardial disease are that there is a widely split second sound occasionally described as an opening snap, there is rather severe splenomegaly, and no fourth heart sound is described. Furthermore, a presystolic gallop, not described in this case, would be more diagnostic of a patient with severe myocardial disease than the accentuated third tone which usually indicates volume overload.

The probability, therefore, is that she does not have any of these myocardial diseases. We should return to a consideration of valvular disease and make a few assumptions about the physical findings and try to get some help from the electrocardiogram. The latter suggests that we are dealing with right ventricular and left atrial hypertrophy. Assuming this to be true, I would suspect that the entire cardiac impulse was made up from the right ventricle and that the widely split second sound was indeed not a widely split second sound but a closely split second sound followed by an opening snap. The patient was in such severe failure at the time of admission that the diastolic rumble usually associated with mitral stenosis was no longer audible. This would lead me to make the diagnosis of mitral stenosis and insufficiency with a systolic thrill at the apex in the face of only minimal insufficiency. On the basis of this assumption and with the findings of bad teeth, a febrile illness, and an enlarged spleen, I would have to consider a diagnosis of bacterial endocarditis. As a matter of fact, it is the only diagnosis which I can make in this patient. I can now combine myocardial disease and valvular disease to explain the findings and the outcome in this patient. I would say that she did indeed have an opening snap, and she probably had had mitral stenosis for some years prior to the time at which she developed bacterial endocarditis. With the development of bacterial endocarditis on the mitral valve, the murmur of mitral insufficiency was produced without necessarily leading to severe mitral insufficiency. The fact that the murmur radiated so well toward the back and not up toward the base of the heart would suggest that the lesion involved the anterior leaflet, directing the regurgitant jet posteriorly into the left atrium so that it could be heard well below the scapula. This could have been associated with some tricuspid insufficiency on the basis of severe failure which developed in conjunction with the overload of the heart produced by the valvular lesion plus the myocardial lesion of bacterial endocarditis. It would also explain the monocytosis and the high sedimentation rate.

There is one other entity, however, which should be mentioned—atrial septal defect of the ostium primum type with a mitral cleft. Again, one would have to assume that bacterial endocarditis had developed on the mitral valve. This would account for the widely split second sound and for the third sound over the right ventricle, and it would

account for the indeterminate axis on the electrocardiogram. I mention this only in passing since the differential diagnosis between ostium primum with mitral cleft and mitral insufficiency on a rheumatic basis is one which should be made only after examination of the patient, for in cardiology as in bridge one peek is worth two finesses.

DR. GREENFIELD: Four views of the chest with barium in the esophagus show the heart shadow to be moderately enlarged with probable biventricular enlargement. No disproportionate left atrial enlargement is seen. There is slight prominence of the main pulmonary artery and prominence of the hila.

The bronchial and pulmonary vascular markings are accentuated and several Kerley "B" lines are seen in the bases of the lungs. Blunting of both costophrenic angles and mild thickening of the pulmonary fissures, probably due to pleural effusion, are noted. There is no evidence of pulmonary infiltration. The bony structures are intact. There is medial and downward displacement of the gastric air bubble, which finding raises the possibility of an enlarged spleen.

Therefore, there are moderate cardiomegaly of a nonspecific type, pulmonary vascular congestive changes, prominent pulmonary arteries and hila, and mild pleural effusion.

STUDENT: Are you bothered by the low voltage in the electrocardiogram, the absence of peripheral edema, and the absence of distention of the cervical veins? How often do you see an enlarged liver 11 cm. below the costal margin without distention of the cervical veins?

DR. GUNNAR: If there were no cardiac failure at all, I would have to assume that some other process caused the dyspnea and involved the heart, liver and spleen, such as sarcoidosis. I would rather assume that the distention of the cervical veins was missed in the examination, since this would be more likely than the probability that the clinical description was not one of cardiac failure.

DR. KRAKOWER: Postmortem examination reaffirmed the absence of peripheral edema and the lack of significant enlargement of peripheral lymph nodes. However, there was clear, straw-colored fluid in the serous cavities: 60 c.c. in the peritoneal cavity, 100 c.c. in the left pleural space and 700 c.c. in the right pleural space, and 50 c.c. in the pericardial sac. The heart was enlarged. It weighed 500 grams. The apex was formed by the left ventricle and the cardiac enlargement was predominantly on the left side. The visceral pericardium was slightly thickened, roughened and granular. Tan-yellow subepicardial infiltrates with an altered fine vascular pattern were apparent, particularly posteriorly. The right atrium was rather small, with normal pectinate muscles, fossa ovalis, coronary ostium and endocardium. In the fixed state, it measured 2 to 2.5 cm. in superoinferior diameter in contrast to the left atrium, which measured 3 to 3.5 cm. in the same diameter. The tricuspid ring measured 12.0 cm. It was within normal range. The leaflets of the tricuspid valve were not remarkable. The right ventricle was somewhat dilated. In the fixed state, the inflow tract measured 6.5 cm. and the outflow 7.8 cm., whereas in the left ventricle the inflow tract measured 8.5 cm. and the outflow 9.8 cm. Subendocardial tan-yellow infiltrates were best seen on the anteroseptal and septal aspects of the pulmonary infundibulum. There was, at best, slight thickening of the trabeculae carneae and papillary muscles of the right ventricle. However, the wall of the right ventricle measured 3 to 4 mm. near the base (normal, 2 to 3 mm.) and up to 6 mm. in the superior septal portion, where tan-yellow myocardial infiltration was clearly evident. The pulmonic valve measured 6.5 cm. in circumference (normal, 8.5 cm.). Its cusps were normal. There was some thickening of the wall of the pulmonary artery but no particular widening. There were no thrombi or emboli in the pulmonary artery or its branches. The wall of the left atrium was thickened up to 3 mm. (normal, 1 to 2 mm.). This was associated with tan-yellow infiltrates. The left atrium was not particularly enlarged and its endocardium was intact. The mitral ring measured 9.5 cm. (normal, 10 cm.). The leaflets of the mitral valve were normal. The left ventricle was dilated. There were subendocardial infiltrates, particularly in the outflow tract, similar to those in the infundibulum on the right. There were no mural thrombi. The myocardium was thickened, ranging from

0.5 cm at the apex up to 1.6 cm at the base (normal 0.8 to 1.0 cm). However the papillary muscles were not particularly thickened. The aortic ring was 6.5 cm in circumference (normal 7.5 cm). The cusps of the aortic valve were normal. There was a thin atheromatous deposit in the left descending coronary artery for 2.5 cm of its proximal length occupying half the circumference of the vessel. There was a dominant right coronary artery with mild atherosclerosis proximally. The left circumflex coronary was short, with little atheroma. Sections through the myocardium revealed extensive infiltration by tan yellow firm tissue of all parts of the interventricular septum particularly toward the base and the anterior and posterior walls of the left ventricle particularly toward the apex. There was some involvement of the papillary muscles, as well. The infiltrates were discrete but more commonly conflu-



Fig. 3. View of left ventricle with massive transmural infiltration of the myocardium and with streaked and spotted subendocardial infiltrates.



Fig. 4. Mid-section through the left ventricular wall parallel to the endocardial surface emphasizes the extent of the myocardial replacement by sarcoid infiltrates.

ent, completely replacing the myocardium over large areas, including its total thickness (Figs 3 and 4) There was less involvement of the anterior and posterior walls of the right ventricle

The lungs were somewhat heavier than normal (right, 540 grams, normal 360 to 570 grams left, 580 grams, normal 325 to 480 grams) with congested and edematous lower lobes. There were enlarged tracheobronchial and paratracheal lymph nodes, varying from 0.5 to 2.0 cm. in diameter They were succulent reddish brown with a tan-yellow infiltrate in one right hilar node. The liver weighed 1,500 grams (normal 1,500 to 1 800) Portal markings were accentuated with congestion of central lobular areas. At the hilus there were enlarged lymph nodes comparable to those in the pulmonary area Similar enlargement of lymph nodes was seen elsewhere in the abdominal cavity The spleen weighed 300 grams (normal 150 to 200) It was brownish red with multiple small infiltrates 1 to 2 mm in diameter of tan yellow color largely in relation to small splenic follicles. The other organs including the thyroid (weight 15 grams) were normal except for some cortical infiltrates in the kidneys and some subserosal infiltrates in the terminal ileum and cecum

Microscopically the infiltrates were of granulomatous character with epithelioid and giant cells and with a variable component of lymphocytes. In the heart the more discrete and confluent infiltrates were associated with marked fibrosis (Fig 5) Partial step sections through the sinoatrial and atrioventricular nodes were studied These were free of lesions, as were the main bundle branches. However there must have been involvement of the more distal branches, since portions of the subendocardium were so extensively involved that the conduction fibers could not be recognized It is of interest that small myocardial blood vessels were involved occasionally in the granulomatous process. In the lungs there were scattered discrete parenchymal granulomata of miliary size More importantly they frequently and markedly involved branches of the pulmonary artery to a point at which these were almost occluded Discrete, small granulomata seeded the portal spaces of the



Fig 5 Microscopic view of the myocardial infiltrate. Most of the infiltrate is of cellular fibrillar collagenous character Dispersed giant cells are seen Clump epithelioid cells are sparse There is little lymphoid infiltra accompanying the infiltrat

liver splenic follicles, and the peritrabecular tissues of the spleen lymph nodes, cortical areas of the kidney and lightly the external muscular coats of the ileum and cecum There were chronic passive congestive changes in the lungs, with alveolar edema. There was some passive congestion of the liver and more of the spleen The aorta was uninvolved in the granulomatous process

Cultures of the heart, lymph nodes spleen and liver for viral agents, fungi and mycobacteria were all negative. Similarly a careful search for pathogenic agents in appropriately stained sections of the involved organs failed to reveal the presence of organisms. Therefore the disease process can be regarded as Boeck s sarcoid a diagnosis which is supported by the noncaseating character of the granulomata except for a few in the spleen and the predilection of the lesions for branches of the pulmonary artery However no stellate inclusions were seen although there were rare Schaumann bodies in the giant cells.

Generalized sarcoidosis most often affects the lungs spleen lymph nodes, and skin although all organs and tissues may be involved Massive sclerosing sarcoidosis of the myocardium is rare however Porter[1] in 1960 was able to collect 33 cases in which death was due to extensive sarcoid involvement of the myocardium Since then 7 additional cases have been described in the literature

In the present case the degree of involvement of the heart was out of all proportion to that of any of the other organs In fact although the lungs were involved microscopically this was not apparent radiographically There was, however sufficient involvement of the liver and spleen to account in part for their relative or absolute enlargement There can be no doubt that there was left ventricular failure as judged by the degree of chronic passive congestion of the lungs Furthermore the decreased compliance of the left ventricle and involvement of the papillary muscles could account for the third heart sound and the relative mitral insufficiency There is reason to believe that there was little right ventricular failure, however The right ventricle was much less involved than the left, and exhibited rather mild hypertrophy Aside from congestion of the lungs, this hypertrophy could be explained by increased pulmonary resistance associated with the occlusive granulomatous lesions of the pulmonary arterial vessels. There was, too mild passive congestion of the liver However there was sufficient granulomatous involvement of the portal spaces of the liver to have caused some degree of portal hypertension Splenic enlargement could then have been due to a somewhat greater degree of passive congestion in addition to granulomatous as well as diffuse lymphocytic and plasma cell infiltration

Diagnosis Massive sarcoid involvement of the heart

REFERENCE

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Fundamentals of clinical cardiology

Left bundle branch block—A clinical assessment

Part I*

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Introduction

Left bundle branch block has been recorded electrocardiographically for over 50 years but was incorrectly diagnosed as right bundle branch block for about the first 25 years. Eppinger and Rothberger[1] introduced the concept of bundle branch block and studied the problem experimentally in dogs. In their early dog experiments, these workers used an esophageal-anal lead and found that severance of the right bundle resulted in a downward QRS deflection in this lead and that cutting the left bundle caused an upward QRS deflection in the same lead. In 1910 Eppinger and Stoerk[2] discovered several patients in whom the QRS was upright in Lead I and downward in Leads II and III. Since Leads II and III corresponded more closely to the esophageal-anal lead used in the dog experiments, these workers made a diagnosis of right bundle branch block.[4] Eppinger and Stoerk[3] published the first electrocardiograms of bundle branch block in man.

In 1915 and 1916, Lewis and Rothschild and Lewis reinvestigated the subject. They found that in the majority of dogs studied, section of the right bundle resulted in downwardly directed QRS complexes in Leads I, II, and III. Section of the left bundle in dogs always produced curves with the QRS complexes upwardly directed in Leads I, II, and III. They termed such tracings concordant in which the QRS complexes had the same direction in all three leads. In bundle branch block in human beings, the curves usually were found to be discordant, with the QRS complex in Lead I opposite in direction to that in Lead III.

Following these early studies, it was generally accepted that in the electrocardiogram of man a wide QRS complex with a downward deflection in Lead I and an upward deflection in Lead III was due to a conduction defect in the left bundle and was called left bundle branch block or the "uncommon" type of bundle branch block. Also, a wide QRS complex with an upward deflection in Lead I and a downward deflection in Lead III was thought to be due to a lesion in the right bundle and was termed the "common" pattern of bundle branch block or right bundle branch block. In 1920 Oppenheimer and Pardee[7] challenged this electrocardiographic classifica

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tion on the basis of a careful study at autopsy of 2 patients with bundle branch block. These workers found the histologic lesions in the branch opposite to the expected one.

In 1929 and 1930 Barker, MacLeod, Alexander and Wilson reported their classic experiments on an exposed human heart and concluded that the "common" pattern of bundle branch block with an upright QRS complex in Lead I was actually due to a conduction defect in the left bundle. The conclusive proof was offered by Wilson and associates in 1932 with the introduction of the precordial leads.[1] They demonstrated in experimental left bundle branch block that the delay in the onset of the intrinsicoid deflection occurred in precordial leads recorded over the left ventricle.

The early confusion in nomenclature apparently had resulted from the difference in limb lead patterns in dog and in man. The dog's heart is electrically more vertical than that of man. The QRS patterns in Leads V_1 and V_6 in left bundle branch block resemble the QRS patterns in Leads II and III in the canine electrocardiogram, whereas they resemble the pattern in Lead I in the electrocardiogram of human beings.[11,12] Had precordial leads been recorded by the early investigators, much of the confusion might have been eliminated.[11,13]

While working in Vienna in 1929 in the laboratory of Dr Rothberger, who at that time was the leading electrocardiographer of Europe, Dr Johnson McGuire recalls that Rothberger was unwilling to accept the new report of Wilson that in human beings the pattern of right bundle branch block was actually left bundle branch block and vice versa.[11] The reason for Rothberger's interpretation was that after section of the left bundle branch in dogs the electrocardiographic pattern was invariably that which in human subjects had been considered to be right bundle branch block before Wilson's work.

In 1935 Wolferth and Margolies[13] gave additional support to the validity of the new electrocardiographic criteria proposed by Wilson. They studied the heart sounds in bundle branch block, and concluded that the view still generally held at that time that the right bundle was blocked in cases of the electrocardiographic pattern of so-called "common" bundle branch block was incorrect and in fact there was a block of the left bundle.

History of physical signs in left bundle branch block

In 1928 King[14] reported the physical signs in bundle branch block. In what is now recognized as left bundle branch block he observed a triad of signs which he thought was highly suggestive of the diagnosis. These consisted of a visible bifid apex thrust, a palpable bifid apex thrust and feeble heart sounds. He also observed a reduplication of the second sound which when present was striking. In 1932 King and McEachern[15] amplified the earlier report and studied the physical signs in 50 cases of bundle branch block. Again they observed faint or even inaudible sounds at the beginning of systole which they thought constituted a helpful diagnostic sign of bundle branch block. It was their opinion, however, that the entire group of physical signs must be considered to establish a clinical diagnosis. In attempting to illustrate the reduplicated thrust of the apex impulse they fastened a light straw on the chest over the region of the apex impulse.

These same workers recorded apexcardiograms and were able to record a double deflection which occurred during systole and which they thought confirmed the reduplicated systolic thrust visible to the naked eye. They concluded that the double apical thrust occurred independent of atrial systole and was due to some peculiarity of ventricular activity in the presence of bundle branch block.

Dr Johnson McGuire[11] recalls that, as a student at Johns Hopkins Medical School, he saw the double impulse in bundle branch block which Dr John King demonstrated by fastening a straw with adhesive tape to the point of maximal impulse. He remembers vividly that one could readily see the double vibration imparted during cardiac systole.

In 1933 Dr Henry Christian[16] wrote that bundle branch block was often detectable by inspection and palpation as pointed out by King. Christian also incorporated these findings in his text.[1] Dr Harold Levine[18] recalls that during

his internship at the Peter Bent Brigham Hospital. Dr. Christian used to delight in demonstrating the bifid apex impulse in left bundle branch block during Grand Rounds on Saturday morning. Dr. Levine further recalls that, after Rounds were over, he and associates, using a similar broomstraw technique, would show that a similar double impulse could occur in patients with hypertensive heart disease. Dr. Levine has recently commented that he believes that, when these facts are reexamined utilizing presently available techniques, quite a distinct difference may be demonstrated between the double impulse of hypertension and that of bundle branch block.[28]

Etiology

It seems to be well established that the most common etiological types of heart disease associated with left bundle branch block are hypertensive heart disease, coronary or ischemic heart disease, or a combination of these two. Johnson and associates[21] studied a group of 555 patients with left bundle branch block. In their series the most common etiological relationship with left bundle branch block was hypertension, which diagnosis was made in 342 patients. In addition, 122 of these patients had clinical manifestations of coronary heart disease (angina pectoris and or myocardial infarction). A total of 209 patients had coronary heart disease. A total of 429 patients (77 per cent of the series) displayed either hypertension or coronary heart disease or both. There were 48 patients with rheumatic heart disease, 10 with syphilitic heart disease, and 10 with cor pulmonale (presumably accompanied by coronary artery disease). There were 14 cases of various etiologies. Of interest is the fact that 77 patients had no obvious etiological cardiac diagnosis and no important systemic disease. Five of these patients were subsequently studied at autopsy; 3 were found to have severe coronary artery disease, 1 had calcification of the mitral ring, and 1 had so-called idiopathic right ventricular hypertrophy.

Bauer[23] has studied the etiological forms of heart disease in 63 cases of left bundle branch block. Forty-four of these 63 patients had clinical evidence of ischemic heart disease (70 per cent of the series). In 16 patients there was definite evidence of myocardial infarction determined electrocardiographically during periods of normal conduction, either prior to the appearance of left bundle branch block or in patients with intermittent or transient bundle branch block. Forty patients (63 per cent) in his series suffered from hypertensive heart disease, and 30 of these had clear-cut evidence of associated myocardial ischemia. He believes that this may be an important clue to the pathogenesis of the conduction defect. Nine patients of his series had no clinical evidence of either ischemic or hypertensive heart disease. Two had aortic stenosis, 1 aortic incompetence, 1 mitral incompetence, 1 cardiomyopathy, 1 myocarditis, and 1 thyrotoxic heart failure. Bauer[23] further observed that the vast majority of patients with left bundle branch block were found to suffer from hypertension and ischemic heart disease. Although either condition may be complicated by left bundle branch block, he emphasized that it is the combination of the two which is most consistently complicated by left bundle branch block. Left ventricular strain with ischemia, either absolute or relative, of the dilated and hypertrophied myocardium appeared to be the most common background to the development of left bundle branch block.

Conyers, Norris and Scott[22] have studied the etiological types of heart disease associated with complete left bundle branch block in 98 patients who came to autopsy at the Cincinnati General Hospital (Table I). The largest group in the series was that with coronary artery disease with or without myocardial infarction, occurring in a total of 85 patients. Hypertensive cardiovascular disease alone occurred in 4, and the combination of hypertension and coronary artery disease occurred in 40. Less frequent types of heart disease (15 of these also had associated coronary artery disease) encountered in association with left bundle branch block in the series were rheumatic heart disease (8), syphilitic heart disease (4), calcific aortic stenosis (5), primary myocardial disease (1), and primary amyloidosis (1). In 5 cases the etiology was obscure; 3 cases were associated with uremia, 1 with pneumonia, and

Table I. Etiological types of heart disease associated with left bundle branch block. A pathologic study of 98 cases

	Male	*Female*	*Total*
Coronary artery disease without hypertension			
With myocardial infarction	10	7	
Without myocardial infarction	8	5	
			30
Coronary artery disease with hypertension			
With myocardial infarction	8	4	
Without myocardial infarction	17	11	
			40
Hypertension alone	2	2	
			4
Miscellaneous etiology*			
Calcific aortic stenosis	3	2	
Rheumatic heart disease			
(a) Carditis	1	2	
(b) Mitral + or aortic valvular disease	2	3	
Unknown†	3	2	
Syphilitic aortic valvular disease	2	2	
Primary myocardial disease	1		
Primary amyloidosis		1	
			24
			98

*Of the 24 cases in the category of miscellaneous etiology 11 also had associated coronary artery disease with hypertension, and 4 had coronary artery disease without hypertension.

†Three associated with uremia, 1 associated with pneumonia, and 1 associated with obstructive jaundice and tuberculosis.

1 with obstructive jaundice and active tuberculosis.

Primary myocardial disease has been found to be associated with left bundle branch block in a substantial number of cases.[20,21] Wood[4] found 14 per cent of his 250 patients with aortic stenosis to have left bundle branch block. Rarer causes of left bundle branch block include diphtheria, sarcoid involvement of the heart, subacute bacterial endocarditis, syphilitic gumma of the septum, myocardial tumors, etc.[22-27]

Left bundle branch block may occur after surgical resection in cases of hypertrophic subaortic stenosis.[13]

Left bundle branch block is rare in infancy and childhood.[14-22] At the Cincinnati Children's Hospital, left bundle branch block has been encountered in this age group most often in two situations: (1) in cases of primary myocardial disease and (2) after surgery in cases of hypertrophic subaortic stenosis.[22]

Anatomy and pathology of the left bundle branch

Anatomy. The atrioventricular (A-V) node is located in the inferior and distal portion of the interatrial septum, lying between the coronary sinus and the medial leaflet of the tricuspid valve.[28,29] The central fibrous body (trigonum fibrosum dexter) consists of dense collagenous tissue which binds the annuli of the mitral, tricuspid, and aortic valves. The A-V node lies on the right side of the central fibrous body at its junction with the mitral annulus.

The A-V bundle (bundle of His) consists of two portions: the penetrating portion and the branching portion. The penetrating portion of the bundle of His lies in the central fibrous body or its distal extension, the atrioventricular portion of the pars membranacea. The branching portion of the bundle of His passes through the lower portion of the pars membranacea.

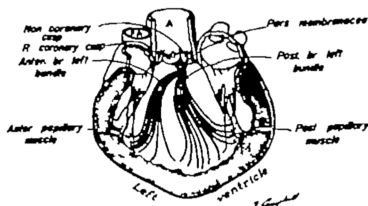


Fig. 1. Diagram of the left bundle branch and its anterior and posterior divisions.

coming to lie near the summit of the muscular interventricular septum.[22-24] As the bundle of His reaches the interventricular portion of the pars membranacea, it begins to give off fasciculi of the posterior radiation of the left bundle branch, thus becoming the branching portion of the bundle (Fig. 1).

In most cases the majority of the fibers destined for the posterior radiation of the left bundle are given off first. These fine fasciculi continue to be given off to about the level of the junction of the right coronary and noncoronary cusps. At this point the bundle bifurcates into the right bundle and the anterior radiation of the left bundle. This bifurcation commonly occurs at the distal angle of the pars membranacea at a point proximal to or at the level of the commissure between the right and posterior aortic cusps (Fig. 1).

The location and manner of bifurcation may vary; in some hearts a bifurcation of the bundle occurs early in its course, at the point at which the left bundle branch fibers begin to arise.[26]

The left bundle branch consists of anterior and posterior radiations of fine fasciculi which fan out beneath the endocardium and become continuous with the Purkinje network.[24] The fibers of the posterior radiation are distributed to the posterior papillary muscle, the mid-septal and apical regions. During their course and at their termination they form a network of Purkinje fibers which enter into the septum and the base and medial aspect of the posterior papillary muscle.[23] The anterior radiation courses in an oblique manner toward the anterior papillary muscle, its medial fibers coursing along the mid-septal and anteroapical region. These fibers likewise form a Purkinje network that terminates in Purkinje fibers which pass into the septum and medial and basal aspects of the anterior papillary muscle[26] (Fig. 1).

The fibers of the A-V node and the bundle of His are distinctly smaller than the myocardial fibers outside the conduction system. The fibers of the left bundle branch at their origin are of the same size as those of the bundle of His. As the fibers proceed distally, they increase rapidly in size until they become larger than those of the ventricular musculature. The left bundle branch and its Purkinje network show more elastic fibers than the ventricular myocardium.[26]

BLOOD SUPPLY TO THE LEFT BUNDLE (FIG. 2). The blood supply to the anterior radiation of the left bundle branch is largely derived from the anterior perforating arteries originating from the anterior descending coronary artery. The blood supply of the posterior radiation of the left bundle is from the posterior perforating branches originating from the posterior descending coronary artery.[26,28]

More specifically, the first part of the left bundle branch is supplied by the ramus septi fibrosi (A-V node artery), the ramus septi ventriculorum superior, and the ramus cristae, which are branches from

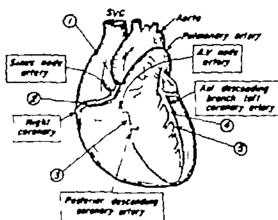


Fig. 2. Diagram of blood supply to the cardiac conduction system. Levels of obstruction of the coronary vessels are indicated by numbers. *1*, Occlusion of the right main coronary artery before the origin of the sinus node artery. *2*, Occlusion of the right main coronary artery distal to the origin of the sinus node artery. *3*, Occlusion of the right main coronary artery distal to the origin of the A-V node artery. *4*, Occlusion of the anterior descending branch of the left coronary artery proximal to the origin of the second perforating branch. *5*, Occlusion of the anterior descending branch of the left coronary artery distal to the origin of the second perforating branch. Note: This diagram depicts the sinus node artery and the A-V node artery originating from the right coronary artery. In about 10 per cent of cases the A-V node artery arises from the circumflex branch of the left coronary artery. The sinus node artery also may arise from the circumflex branch of the left coronary artery in about 10 per cent of cases.

the right coronary artery.[15] The first part of the left bundle also is supplied by the ramus limbi sinistri from the anterior descending branch of the left coronary artery.[15] The second portion of the left bundle is supplied by the anterior and posterior perforating vessels from both the right and left coronary arteries.[15]

Pathology of the left bundle. Mahaim[27] and Yater[4] performed careful histologic studies of the bundle branches in cases of bundle branch block and concluded that lesions of the bundle branches were usually bilateral. Despite the careful nature of these studies, they were performed in patients prior to the era of precordial leads.[21,29]

Lev[24,25] has reviewed the studies correlating lesions in the conduction system with the electrocardiographic pattern of left bundle branch block. Sanabria[43,44] found no correlation between histologic lesions in the bundle branches and the electrocardiographic pattern of bundle branch block. Lenègre and associates[34,35,47] found that the pattern of complete left bundle branch block in 25 cases studied was correlated in two thirds of them with major lesions in the left bundle branch. In 9 there was total destruction, and in 9 there was almost total destruction. The lesions were found to be localized in the very beginning of the left bundle, usually resulting from a fibrous or fibrocalcareous spur-like extension of the membranous septum, suggesting a mechanical rather than an ischemic origin. In one third of their cases, Lenègre and associates[47] found the lesions to be minor or absent. Permanent complete left bundle branch block was found most commonly to be associated with aortic disease, coronary disease, and hypertensive heart disease. Lenègre[47] found that the right bundle in these cases was either normal or showed only minimal involvement, whereas the left bundle was usually involved at its origin. Sometimes the damage occurred more distally.

CORONARY ARTERY DISEASE (FIG. 2). Narrowing or occlusion of the right main coronary artery at its origin before the origin of the ramus ostii cavae superioris (sinus node artery) may produce ischemic changes in the sinoatrial (S-A) node, the A-V node, the bundle of His, the beginning of both bundle branches, and the posterior radiation of the left bundle. Occlusion of the right main coronary artery distal to the origin of the ramus ostii cavae superioris (sinus node artery) and proximal to the origin of the ramus septi fibrosi (A-V node artery) may result in similar changes while sparing the S-A node.[*] Occlusion of the right main coronary artery beyond the origin of the ramus septi fibrosi may produce ischemic changes in the posterior radiation of the left bundle branch. Narrowing or occlusion of the anterior descending coronary artery in its

* In about 10 per cent of patients the A-V node artery arises from the circumflex branch of the left coronary artery.[15]

† In about 10 per cent of patients the sinus node artery arises from the circumflex branch of the left coronary artery.[15] In these cases, occlusion of the right main coronary artery would spare the sinus node.

first portion proximal to the origin of the second perforating branch may produce ischemic changes in the anterior radiation of the left bundle branch as well as in the mid portion of the right bundle branch. Narrowing of the anterior descending coronary artery distal to the origin of the second anterior perforating vessel may produce ischemic changes in the anterior radiation of the left bundle branch alone. As emphasized by James and Burch [illegible] specific alterations in conduction depend upon the efficiency and extent of collateral circulation

It is important to emphasize that complete disruption of the left bundle branch implies an extensive lesion involving the beginning of the left bundle branch which requires narrowing of both the right and the left coronary arteries[11, illegible] (Fig 2)

The left bundle may be involved at its origin by sclerosis of the summit of the ventricular septum of the pars membranacea and the central fibrous body or by endocarditis of the aortic valve.[illegible] Lev has further emphasized that the subendocardial position of the left bundle in a heart chamber with high pressure may make it more vulnerable to sclerosis at the base especially in patients with systemic hypertension

Blondeau Rizzon and Lenègre[illegible] have observed that in both anterior and posterior myocardial infarction, lesions of the A-V node and bundle of His are less severe than those of the distal bundle and of the bundle branches.

Lev[38] has emphasized that with advancing age there is progressive fibrosis and calcification of the mitral annulus, the central fibrous body the pars membranacea the base of the aorta, and the summit of the muscular ventricular septum He has designated this as sclerosis of the left side of the cardiac skeleton and has found that this process first appears at the age of about 40 years. He thinks that it is perhaps the most common cause of permanent complete A-V block but may also result in left bundle branch block [illegible]

Other pathologic processes may involve the left bundle It may be involved in myocarditis, endocarditis, primary myocardial disease rheumatic heart disease and rarely syphilitic heart disease

Lev[44] has reported on a patient with complete left bundle branch block who physiologically showed no delay in the onset of ventricular systole but delay in the onset and termination of ventricular ejection. Pathologic examination of the conducting tissue showed a severe lesion of the origin of the left bundle, produced by fibrosis and scarring of the central fibrous body the pars membranacea and the base of the interventricular septum This patient had a congenital malformation of the aortic valve with aortic insufficiency which had led to the focal endocardial fibroelastosis of the left ventricle with severe fibrosis at the beginning of the left bundle branch

Detailed pathologic findings in cases of left bundle branch block

In the Department of Pathology at the Cincinnati General Hospital (as part of an extensive anatomic-electrocardiographic correlation study) the hearts of 9 patients with the typical electrocardiographic pattern of complete left bundle branch block have been examined utilizing a dissection technique which yields precise determinations of muscle mass for each of the cardiac chambers[47] (Table II) Severe cardiac hypertrophy principally involving the left ventricle but affecting all chambers, was present in 7 In these 7 cases the average weight of the undissected heart was 793 grams, and the average weight of the free left ventricular wall plus the interventricular septum was 380 grams, approximately twice the maximum normal value. Coronary arteriosclerosis was severe in 2 (*A 31 A 104* Table II) of the 7 cases exhibiting marked hypertrophy and in both instances was associated with severe myocardial fibrosis. In 5 of the cases with massive cardiomegaly however *classic* complete left bundle branch block was not associated with severe coronary sclerosis. Furthermore anatomic evidence of severe coronary insufficiency (i.e. extensive myocardial fibrosis) was not a prominent feature in these cases.

In the other 2 cases (*A 2 4-88* Table II) left ventricular hypertrophy was minimal but each exhibited severe coronary arteriosclerosis. Focal areas of healed

grades of left bundle branch block first second and third degrees. The first two correspond to what is generally accepted as incomplete left bundle branch block, and his third grade or so-called advanced left bundle branch block conforms to what is usually considered complete left bundle branch block. Katz and associates[17,61] prefer the term intraventricular (left bundle branch system) block

This paper is concerned primarily with the entity that has been termed complete left bundle branch block. The findings in so-called incomplete left bundle branch block will not be described except where they may be of importance in the differential diagnosis from complete left bundle bran h block.

Anterolateral peri infarction block with QRS prolongation[9,62] may not infrequently be confused with complete left bundle branch block The differential electrocardiographic features have been well described by Grant[62,63] and have recently been reviewed[64]

Ventricular activation

Normal heart (*Fig 3*) The current concepts of ventricular activation in the normal heart have recently been reviewed[62] The first portion of the left septal surface to be normally activated is the middle third The apical portion of the septum near the anterior and the posterior borders is activated about 0 01 sec after the initial portion The left septal surface completes its activation in about 10 to 15 milliseconds. The last region to be activated is the posterobasal portion

The first portion of the right septal surface to be activated is the inferior third in the region of the anterior papillary muscle, where the right bundle branch begins to ramify The initial activity on the right septal surface occurs about 0 005 to 0 015 sec after the initial activation of the middle third of the left septal surface The right septal apex is activated 0 005 to 0 01 sec later The remainder of the right septal surface is activated from below upward the last area to be activated being the posterobasal portion of the right septal surface

The interventricular septum is activated from both sides toward the center although most workers agree that the preponderance of excitation is from the left to right Septal activation is usually complete in about 0 025 sec Sodi Pallares[64] and Medrano and associates[64] have demonstrated that the bulk of the septal mass is normally activated through the left bundle and the right septal mass normally activated by the right bundle is only about one third to one fourth that of the left septal mass These workers believe that the right and left septal masses are electrically independent and that there is a so-called electrical barrier between them

The apex of the free wall of the left ventricle undergoes activation about 0 01 sec after the initial depolarization of the middle third of the left septal surface From the region of the apical endocardium

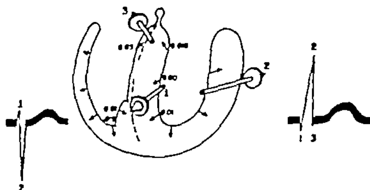


Fig 3 Vector representation of the main forces of ventricular acti tion in the normal heart (adapted from Sodi-Pallares et al.[64]).

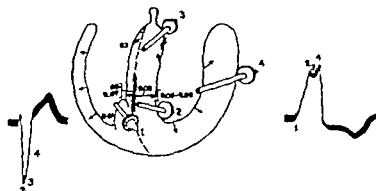


Fig. 4. Vector representation of ventricular activation in left bundle branch block (adapted from Sodi-Pallares et al.[44]).

the impulse spreads rapidly to the entire left ventricular endocardium.

VECTOR REPRESENTATION OF THE MAIN CARDIAC FORCES (FIG. 3). The initial activation can be represented by a vector directed from left to right, arising from the mid-portion of the left septal surface pointing anteriorly and toward the trabecular zone and apex of the right ventricle and to the anterior papillary muscle on the right septal surface. This initial septal vector produces the normal Q waves in Leads V_5 and V_6 and the small R waves in Leads V_1 and V_2. The second major cardiac force can be represented by a vector corresponding to activation of the free left ventricular wall. This vector is directed leftward, posteriorly, and either somewhat upward or downward depending upon the position of the heart. This second cardiac vector corresponds to the tall R waves in Leads V_5 and V_6 and the deep S waves in the right precordial leads.[44]

The last portion of the heart to be activated is the posterobasal region of both ventricles and the posterobasal portion of the interventricular septum. This force can be represented by the third cardiac vector which is directed posteriorly, superiorly, and toward the right.[47]

Activation of heart in complete left bundle branch block (Fig. 4). This topic has also been reviewed recently.[48] The first portion of the heart to be activated in complete left bundle branch block is the lower third of the right septal surface in the region of the anterior papillary muscle. The remainder of the right septal surface is activated from below upward in a normal manner. The impulse spreads across the interventricular septum from right to left. From this point there is lack of agreement by different investigators concerning the spread of activation[44] (Fig. 5).

According to Sodi-Pallares[44] and Medrano and associates,[44] there is initially a delay at the boundary between the right septal mass and the left septal mass (Figs. 4 and 5,*a*). This so-called "barrier" is

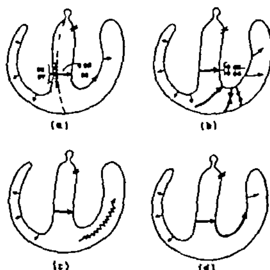


Fig. 5. Proposed mechanisms of ventricular activation in left bundle branch block (see text). *a*, Mechanism proposed by Sodi-Pallares et al.[44] *b*, Mechanism proposed by Becker, Scher and Erickson.[49] *c*, Mechanism proposed by Bryant[50] and Grant.[49] *d*, Mechanism proposed by Barker.[51]

thought to be about millimeters in thickness and near the right septal surface. The delay here lasts from 0.02 to 0.04 sec, although recently Medrano[11] has reported a delay of up to 0.06 to 0.0 sec. The left septal mass is then activated from right to left, the spread taking about 0.03 sec. The propagation of the impulse in the reverse manner from right to left through the left septal mass is thought to occur through muscle fibers rather than through the Purkinje system. The delay in arrival of the impulse at the left septal surface is from 0.05 to 0.08 sec. The more superior portion of the left septal surface shows more delay than do the middle and lower portion. These workers have found that once the impulse has reached the left septal surface the activation of this surface and the free left ventricular wall proceeds through the Purkinje network at a normal rate and in a normal direction. Sodi-Pallares and associates attribute the QRS prolongation not only primarily to the delay at the "barrier" between the right and left septal masses but also to some delay in spread through the left septal mass itself.

Becker and associates have studied the spread of ventricular excitation in experimental left bundle branch block. They found that during the first 0.015 sec there is depolarization of the tissue normally activated by the right bundle, i.e., the right septal and right ventricular myocardium. The interventricular septum is then activated smoothly by muscle conduction from right to left with no evidence of intraseptal delay. Septal activation was found to take from 0.05 to 0.06 sec (Fig. 5,b). They also found that by this time ventricular activation had extended to both anterior and posterior epicardium and that in the anterior septal region there was epicardial-to-endocardial spread by muscle conduction. With the activation of the left septal surface the wave front spread endocardially and depolarization began in the free wall bordering the cavity. During the time from 0.06 to 0.07 sec the wave front moved laterally and the impulse entered the endocardial conduction network, initiating endocardial-to-epicardial spread with activation in most of the left lateral free wall (Fig. 5,h).

Other workers have attributed the QRS prolongation to the slowed right-to-left septal depolarization plus a delay in the activation of the left ventricular free wall because of an abnormal route of activation, i.e., the wave entering the mural myocardium and spreading directly without passing through the Purkinje system[1,2,11] (Fig. 5,c).

A fourth school believes that there is a slow but uniform spread of activation across the interventricular septum from right to left. Once the impulse has reached and entered the intact left bundle below the level of block, there is then normal activation of the left ventricular free wall through the conduction network (Fig. 5,d).

VECTOR REPRESENTATION IN LEFT BUNDLE BRANCH BLOCK (FIG. 4). *In left bundle branch block the initial vector of septal depolarization is thought to correspond to the activation of the mid portion of the right septal mass.* It is directed from the lower third of the right septal surface to the left, inferiorly, and usually somewhat anteriorly (occasionally slightly posteriorly).[13] This vector produces the initial upstroke in Lead V_5, V_6, and I. The second vector represents the depolarization of the left septal mass in the lower portion of its middle third from the interseptal "barrier" to the lower portion of the left septal surface near the papillary muscle. It is directed posteriorly from right to left and somewhat inferiorly, although occasionally it may be directed upward. This is thought to account for the major portion of the R wave in Leads V_5 and V_6, and the downstroke in Leads V_1 and V_2.

The third vector of septal depolarization is located in the middle *and upper thirds of the left septal mass and is oriented from right to left,* superiorly, and posteriorly. The latest portion of the left septal mass to become depolarized is the anterior basal portion. As the activation process approaches the endocardium of the left septal surface it is quite slow. This is now thought by Sodi-Pallares and his associates[4] to give rise to the major portion of the slurring and notching of the R waves in Leads V_5 and V_6 and the slurring of the S waves in the right precordial leads. The notching and slurring and slowing have been attributed to two *factors*: (1) the crossing of the electrical "barrier" at dif

ferent levels in the septum and (2) the reversed activation from muscle fiber to Purkinje fiber in the left septal mass.[8]

The fourth vector represents the activation of the free left ventricular wall and is directed to the left posteriorly and either superiorly or inferiorly and is thought to account for the second peak of the R wave in the left precordial leads and Lead I and the final portions of the S wave in the right precordial leads. Evidence has also been presented that the activation of the free left ventricular wall may actually add little to the QRS complex in left bundle branch block.[6]

Repolarization in left bundle branch block

In left bundle branch block, septal repolarization or recovery is directed from right to left.[4] The repolarization vector is opposite in direction to the repolarization or recovery sequence.[8] The repolarization vector is thus directed from left to right resulting in negative T waves in leads over the left ventricle (V_5, V_6) and positive T waves in leads over the right ventricle (V_1, V_2).

Vectorcardiogram

Normal vectorcardiogram. It has been repeatedly demonstrated and is now generally agreed that the corrected orthogonal lead systems are superior to the older systems, such as the cube and tetrahedron in accurately displaying the electrical forces of the heart. At the present time, the Frank[72] lead system is the most widely accepted because it is not only a reasonably accurate orthogonal lead system but also because of the comparative simplicity of recording.

The comments that follow concerning the normal vectorcardiogram are based primarily on those studies employing the Frank lead system,[74-77] although studies

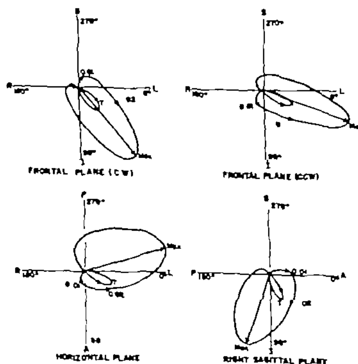


Fig. 6. Diagrams of the QRS and T loops in the normal vectorcardiogram in the frontal, horizontal, and right sagittal planes. *S*, Superior; *I*, Inferior; *P*, Posterior; *A*, Anterior; *R*, Right; *L*, Left; *CW*, Clockwise rotation; *CCW*, Counterclockwise rotation; *T*, T loop; *0.01*, 0.01 sec. QRS vector; *0.02*, 0.02 sec. QRS vector; *Max*, Maximum QRS vector.

somewhat posteriorly. The T loop in the right sagittal plane is inscribed in a clockwise direction and the maximal T vector is directed inferiorly and usually anteriorly.

Vectorcardiogram in left bundle branch block. As in the case of the normal vectorcardiogram, most of the observations in this paper concerning the vectorcardiogram in left bundle branch block are based on studies conducted with the corrected orthogonal lead system of Frank,[34,73] although here again other studies not performed with the Frank lead system were also consulted.[31,64,84,75]

HORIZONTAL PLANE (FIGS. 7-10). The initial forces of the QRS loop in the horizontal plane in left bundle branch block are directed anteriorly and to the left[64,43,73] (Figs. 7, 8, 9, 10,*A*). This initial component of the vectorcardiogram has been attributed to the earliest forces of ventricular depolarization which occur in the region of the anterior papillary muscle of the right ventricle in the region of the attachment of the free wall to the interventricular septum.[64,73] Sodi-Pallares and associates[73] attribute this initial right-to-left and anterior spread to the activation of the middle portion of the right septal mass.

The initial 0.01 sec. vector in left bundle branch block has been considered to be the resultant of two component vectors: (1) the right ventricular vector directed anteriorly, rightward, and inferiorly corresponding to early activation of the free wall of the right ventricle adjacent to the septum and (2) a septal vector directed to the left, inferiorly, and posteriorly corresponding to the early activation of the septum from right to left. If the free wall component vector should dominate, the initial 0.01 vector may be directed slightly to the right as well as anteriorly (Fig. 10,*A*). This configuration is less frequent in left bundle branch block than is the initial anterior and leftward inscription.[43,73,7]

The initial anterior and leftward forces in the vectorcardiogram correspond to the initial small R waves in Lead V_1 and the initial upstroke in Lead V_6 in the electrocardiogram. In those less common cases of complete left bundle branch block in which the initial forces are directed both anteriorly and slightly rightward, small Q waves are inscribed in Leads I, aVL, and in V_6[64] (Fig. 10,*A*).

In a minority of patients with complete left bundle branch block, the initial forces are directed leftward and posteriorly with no anterior component[73,64] (Fig. 10,*B*). In these cases, without myocardial infarction, the initial leftward and posterior orientation has been attributed to dominance of the septal component of the initial 0.01 vector. Such patients have no initial R waves in the right precordial electrocardiographic leads.

To summarize, the initial 0.01 forces in left bundle branch block are most commonly directed anteriorly and leftward and are written in a counterclockwise direction.

After the initial forces are inscribed there is then an abrupt change in direction with the major portion of the QRS loop in the horizontal plane being inscribed posteriorly and to the left and in a clockwise direction (Figs. 7 and 8). The efferent or centrifugal limb is written rather quickly but there is a distinct slowing of inscription near the midpoint of the QRS loop and a most conspicuous slowing during the inscription of the initial half of the afferent limb of the loop.[73] The length of the loop and the length-to-width ratio of the loop are significantly increased in the horizontal plane in left bundle branch block.[73] The QRS loop usually does not return to the isoelectric point, there being J displacement to the right and anteriorly. The T loop is usually oriented rightwardly, anteriorly, and about 180 degrees from the long axis of the QRS loop[43,64] (Figs. 7-9). The mean QRS axis in the horizontal plane is directed leftwardly and posteriorly, ranging from −55 to −85 degrees (+305 to +275 degrees).[73] Some cases of uncomplicated left bundle branch block will display a figure-of-eight of the QRS loop in the horizontal plane (Fig. 9).

FRONTAL PLANE (FIGS. 7-9). The initial forces in the frontal plane are usually directed to the left and inferiorly more commonly than superiorly.[73] An initial rightward force in the frontal plane is ordinarily absent in left bundle branch block.[73] The QRS loop in the frontal plane is usually inscribed in a counterclockwise direction and is delayed in inscription

The magnitude of the QRS loop in the frontal plane is greater than normal; the length generally is not increased but the width is greater than normal. There is usually J displacement to the right and inferiorly.[6,7] The maximal QRS vector in the frontal plane was found by Wallace and associates[12] to be +2 ± 6 degrees using the Frank system and by Maize and Walsh using the cube system to range from −15 to +40 degrees (+345 to +40 degrees) with an average of 0 degrees. The T vector in the frontal plane is usually displaced 180 degrees from the maximal QRS vector. The T vector then points rightwardly in the frontal plane.[11]

RIGHT SAGITTAL PLANE (FIGS. 7-9). The initial forces in the right sagittal plane are

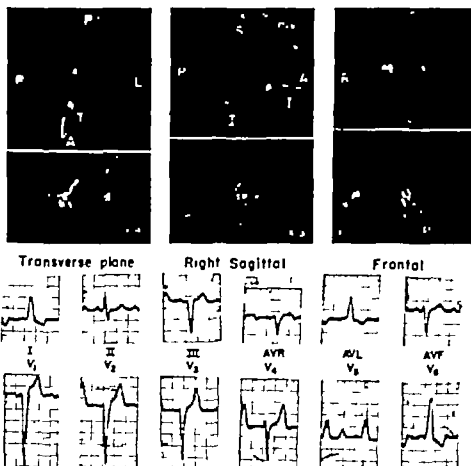


Fig. 8. Patient K. M. Left bundle branch block. *Vectorcardiogram:* Transverse (Horizontal) Plane—The initial vectors are directed to the left and anteriorly. The major portion of the QRS loop is inscribed in a clockwise direction; the general direction of the QRS loop is posterior and slightly to the left; the mid and late portions of the QRS loop are slowly inscribed. The T loop is discordant (oriented in a direction opposite to the QRS loop). The ST vector is directed anteriorly and slightly to the right. Right Sagittal Plane—The QRS loop is inscribed clockwise with a rather small initial anterior force; a conduction delay in the mid and late portion can also be seen. The T loop is discordant to the QRS loop. The ST vector is directed anteriorly. Frontal Plane—The QRS loop is inscribed in a counterclockwise direction. There is slowing of the mid and late portions of the QRS loop. The early portion of the QRS loop also appears to be slowly inscribed, but this is actually due to foreshortening of the loop because of its posterior orientation. The T loop is discordant to the QRS loop. The ST vector is directed to the right. Spatial QRS Loop—The QRS-E loop is directed posteriorly and slightly toward the left; the early part is inferior and the terminal part is superior; the mid portion and late portion are slowly inscribed. *Electrocardiogram:* Typical pattern of left bundle branch block. QRS duration 0.12 sec. Broad, monophasic R waves in Leads I, V_5, V_6. Small R waves in right precordial leads. No Q waves in Leads I, AVL, V_5 and V_6. Secondary S-T segment and T-wave changes. (By courtesy of Dr. T-C Chou.)

usually anteriorly and inferiorly directed.[71] The QRS loop in this plane rotates in a clockwise direction and the maximal QRS vector is directed posteriorly, being found by Wallace and associates[72] to be $+169 \pm 10$ degrees, using the Frank system, and to range from $+60$ to -175 degrees ($+185$ degrees), with an average of $+150$ degrees, by Mamre and Walsh.[81] The magnitude of the QRS loop in the right sagittal plane is distinctly increased over normal with the length of the loop and the length-to-width ratio of the loop being significantly increased.[72]

Wallace and associates[72] found that the QRS loop in the right sagittal plane, after

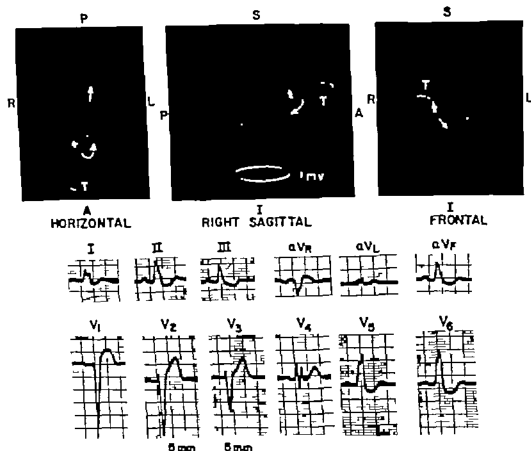


Fig. 9. Patient N.S. Left bundle branch block. *Vectorcardiogram*: Horizontal Plane—The initial vectors are directed to the left and anteriorly. The main body of the QRS loop has a figure-of-eight configuration; the QRS loop is oriented posteriorly and slightly to the left; the mid and terminal portions of the loop are slowly inscribed. The T loop is directed anteriorly and the ST vector is directed to the right and anteriorly. Right Sagittal Plane—The initial vectors are directed anteriorly. The QRS loop is inscribed clockwise and is oriented posteriorly; the mid and terminal portions are slowly inscribed. The T loop and ST vector are opposite in direction to that of the QRS loop. Frontal Plane—The initial vectors are directed to the left and inferiorly. The QRS loop is inscribed counterclockwise; there is notching of the mid-portion of the loop. The slow inscription of the mid and terminal portions of the loop is also seen. The T loop and the ST vector are directed opposite to the QRS loop. Note that the J point is displaced rightward and superiorly. Spatial QRS loop—The QRSsÊ loop is oriented posteriorly and to the left. The initial vectors are directed to the left, anteriorly, and inferiorly. In the horizontal plane the QRS loop has a figure-of-eight configuration, and in the frontal plane it is inscribed counterclockwise. The mid and terminal portions of the loop are slowly inscribed. The ST vector and TsÊ loop are opposite in direction to that of the QRSsÊ loop. *Electrocardiogram*: Typical pattern of left bundle branch block. QRS duration 0.12 sec.; broad, monophasic notched R waves in Leads I, V_5, V_6. No Q waves in Leads I, V_5, V_6. Secondary S-T segment and T-wave changes.

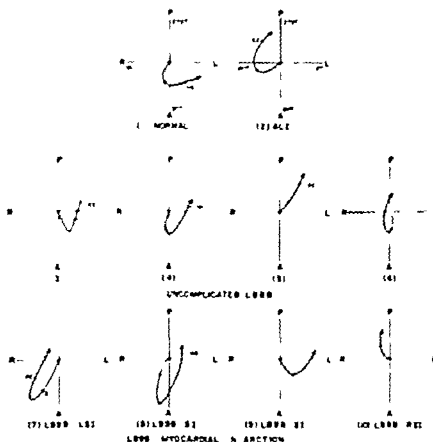


Fig. 10. Diagram of the initial QRS forces in the horizontal plane. 1, Normal. [illegible] 3-6, Uncomplicated left bundle branch block. 7, Left bundle branch block plus left septal infarction. 8, Left bundle branch block plus septal infarction. 11, Left bundle branch block [illegible] septal infarction. P, Posterior. A, Anterior. R, Right. L, Left. [illegible] 0.01 sec. QRS [illegible] 0.0 sec. QRS [illegible] 0.03-0.04 sec. QRS [illegible]

the initial inscription usually moved posteriorly and inferiorly and ordinarily rotated in a clockwise direction although they found that a lesser number displayed a figure-of-eight rotation and there was one case with counterclockwise inscription. The J point is usually displaced anteriorly and inferiorly. The T loop in this plane also lies approximately 180 degrees removed from the major QRS axis, being directed anteriorly.

Correlation of the vectorcardiogram with the four main vectors in left bundle branch block (Figs. 4 and 7). Just as there is lack of agreement on the mechanism of the spread of activation in left bundle branch block in the experimental studies,[48] so there is lack of precise agreement on the correlation of the vectorcardiogram with the representation of the four main cardiac vectors in left bundle branch block. No attempt will be made to reconcile these views in this communication, but merely to recount them briefly.

The first main vector is directed from right to left and usually anteriorly and inferiorly (Fig. 4). Sodi-Pallares relates this to the activation of the middle portion of the right septal mass and the passage of the activation wave from the right septal mass to the left septal mass and correlates this with the initial forces in the vectorcardiogram which are usually directed anteriorly and to the left (Fig. [illegible]). Wallace and co-workers,[77] correlating their findings with the experimental studies of Becker, Scher and Erickson, relate the first vector to the initial anterior forces recorded from the anterior paraseptal portion of the right ventricle and relate

this to the initial forces of the vector cardiogram.

The second vector according to Sodi-Pallares and associates,[41] represents activation of the left septal mass in the lower portion of its middle third from the interseptal barrier to the endocardial surface of the left side of the interventricular septum near the papillary muscle. This vector is directed leftward posteriorly and downward (Fig 4). They correlate this with the first part of the R loop or the efferent limb of the vectorcardiogram, which is directed posteriorly and to the left (Fig 7). Wallace Estes, and McCall[72] attribute this vector also to predominant right-to-left activation of the interventricular septum and to the efferent limb of the QRS loop.

The third vector according to Sodi Pallares and associates[41] is also a septal vector due to activation of the left septal mass in its mid and upper thirds. The vector is directed leftward superiorly and posteriorly (Fig 4). They point out that the latest portion of the left septal mass to become depolarized is the anterior basal portion, and that the activation wave is unusually slow as it approaches the endocardium of the left septal surface. They attribute this slow activation as an explanation of most of the slurring and notching of the R wave in Leads V_5 and V_6 and the slow inscription of the distant portion or afferent limb of the vector cardiogram (Fig 7). Wallace and associates[72] attribute the third vector to be the resultant of the terminal forces within the septum plus the epicardial-to-endocardial spread of the forces of the free wall of the left ventricle in the anterior septal region, which has been experimentally demonstrated by Becker Scher and Erickson[3] (Fig 5,b).

Both Sodi Pallares[4] and Wallace[72] agree that the fourth vector represents activation of the left ventricular free wall with depolarization proceeding from endocardium to epicardium (Fig 4). This vector corresponds to the returning limb or the afferent portion of the loop (Fig 7). Sodi Pallares associates this fourth vector with the second peak of the R wave in Leads V and V_6. Wallace[72] has observed that there is significantly less slowing in the terminal portion of the afferent limb of the QRS loop and has related this to more normal endocardial-to-epicardial spread during the later stages of activation of the left ventricular free wall.

Other workers[71,74] have made other slightly different temporal correlations between the vectorcardiogram electrocardiogram and the vector forces.

Ventricular gradient in left bundle branch block

Burch and DePasquale[75] have studied the ventricular gradient in 77 patients with left bundle branch block. The ÂQRS was located to the left and superiorly the mean vector being in the first sextant, with a mean direction of −17 degrees and a magnitude of 67 microvolt seconds. The ÂT was located inferiorly and to the right with a mean direction of +135 degrees and a mean magnitude of 44 microvolt seconds. The ventricular gradient (Ĝ) was located to the left and somewhat inferiorly with the mean direction of +0.5 degrees and a mean magnitude of 39 microvolt seconds. The ventricular gradient in their cases of left bundle branch block was somewhat shorter and further to the left than the mean normal ventricular gradient (46 2 microvolt seconds).

In their series of 77 patients with left bundle branch block, 32 had associated left ventricular hypertrophy. The ventricular gradient, ÂQRS and ÂT in these 32 were essentially the same as those for the over-all group. The ventricular gradient in 15 patients with left bundle branch block and myocardial infarction was similar to that found in patients with left bundle branch block and left ventricular hypertrophy except for a slight rotation of the ÂQRS and Ĝ to the right in the group with myocardial infarction.

Pantridge[77] determined the ventricular gradient in 18 patients with left bundle branch block and found it to be normal in those with minimal heart disease and abnormal in those with more serious underlying myocardial disease.

Sodi Pallares and associates[44] have also studied the ventricular gradient in left bundle branch block. In uncomplicated left bundle branch block they found the position of the ventricular gradient (usu-

ally ranging from −1 to +56 degrees) to be normal. They found that an abnormal gradient in patients with left bundle branch block commonly signified complicating ischemia or some other type of myocardial alteration.

Computer analysis in left bundle branch block

Lipberger, Stallmann and Berson[34] analyzed the orthogonal electrocardiogram in 56 cases of left ventricular conduction defect by means of an automatic procedure employing a digital computer. Most spatial vector direction including polar QRS vectors, SAT, SVC and instantaneous QRS vector obtained after two eighths and three eighths of the total QRS duration were abnormal. Abnormalities of spatial magnitude were most frequent in SAQRS and SAT.

Preliminary observations in cases of left bundle branch block using a computer program similar to Lipberger's have been made in our laboratory.[35]

Auscultation

Normal heart sounds. The first heart sound has been shown phonocardiographically to consist of four components. The first and fourth are of low frequency and are usually inaudible. The second and third components are of higher frequency and are audible.[47,48] Leatham[4] has demonstrated that mitral and tricuspid closures are mainly responsible for the first sound. The two major components of the first sound are ordinarily separated by a narrow interval of 0.02 to 0.03 sec.; mitral closure normally occurs before tricuspid closure. The splitting of the first sound is attributed to the normal slight asynchrony between the left ventricular and right ventricular contraction, the left ventricular contraction preceding that of the right by a brief interval.[7,5]

Although the left ventricle begins to contract before the right, its ejection commences somewhat later and the left ventricular ejection normally ends before right ventricular ejection[5] (Fig. 14 *1*).

The second sound in the normal individual is split, the aortic closure occurring before pulmonic closure. This split is most evident with inspiration, widening to 0.04 to 0.06 sec. or is even longer in young individuals. During expiration the splitting tends to narrow, the second sound even becoming single. The explanation for this physiologic splitting of the second sound is now well accepted. During inspiration there is an increased venous return to the right atrium and right ventricle with a concomitant increase in stroke output and duration of ventricular ejection from the right ventricle. This results in a delay in closure of the pulmonary valve. At the same time there is a diminution of venous return to the left ventricle. There is some shortening of left ventricular systole that results in an earlier closure of the aortic valve. During expiration the venous return to the right heart decreases and pulmonary venous return increases. This results in a single sound in the pulmonary area or a sound split by a narrow interval of about 0.02 to 0.03 sec. (inaudible split).[47,48]

Left bundle branch block

FIRST SOUND. The first sound in left bundle branch block is prolonged and may last more than 0.16 sec.[3] The amplitude or intensity of the first sound may be lower than normal[47,48] (Fig. 11). Bellet[48] attributes the diminished intensity of the first sound in left bundle branch block to a lengthened interval between atrial and left ventricular contraction.

Leatham[3] has commented that one can rarely make good observations on the first heart sound in the presence of left bundle branch block because the sound is usually soft. Presumably this is because there is usually left ventricular disease with powerful atrial contraction and ventricular filling, thus semiclosing the mitral valve before the left ventricle contracts.[37]

Although the earlier workers[17] described splitting of the first sound of pathologic degree in left bundle branch block, more recent stethoscopic phonocardiographic tracings have not confirmed this splitting.[47,48] Luisada[47,48] has pointed out that normally the central phase (audible portion) of the first sound lasts from 0.06 to 0.08 sec. With left bundle branch block even if there is delay in onset of contraction of the left ventricle of 0.04 to 0.05 sec., this is not sufficiently long to cause splitting of the central phase.[4] Lea-

PARADOXICAL SPLITTING OF S_2 IN LBBB

Fig. 11. Phonocardiogram in Patient R. Sh. with left bundle branch block. *The aortic component of the second* heart sound follows the pulmonic component as shown in the first cardiac cycle recorded at the end of expiration. In latter inspiration the pulmonary component of the second heart sound occurs later in the cardiac cycle and fuses with the aortic component producing a single second sound. A nonpansystolic murmur is recorded. The first heart sound is faint and of low amplitude. *ECG-II* Electrocardiogram—Lead II. *PCG* Phonocardiogram. *PA* Pulmonary area. *S* First heart sound. S_2 Second heart sound. P_2 Pulmonic component of second heart sound. A_2 Aortic component of second heart sound. *SM* Systolic murmur.

tham[17] has also observed that the first sound in left bundle branch block is seldom split.

However phonocardiograms have been published which do display distinct splitting of the first sound in some cases of left bundle branch block, with tricuspid closure occurring first and mitral closure occurring some 0.03 sec. later.[18] Levine and Harvey[19] also have a record showing wide splitting of the first sound in left bundle branch block.

McKusick and associates[20] have commented on the first sound in left bundle branch block, emphasizing that normally the closure of the mitral and aortic valves slightly precedes closure of the tricuspid and pulmonary valves. These workers have pointed out that left bundle branch block is less likely to produce splitting because delay in the closure of the mitral valve tends merely to cancel the normal asynchronism. They do further observe, however, that it is difficult to understand why the first heart sound is not more frequently and markedly split in cases of bundle branch block. They have also published a phonocardiogram which does show distinct splitting of the first sound in left bundle branch block.

Phonocardiographic recordings from some cases of left bundle branch block (with delay of left ventricular contraction of 0.06 sec. or more) have revealed three groups of vibrations comprising the first sound: the first attributed to tricuspid *closure, the second to pulmonic opening* plus delayed mitral closure, and the third to aortic opening.[12, 18, 19] Burch[18] has described and illustrated these three well developed components of the first sound in left bundle branch block.

SECOND SOUND. In left bundle branch block there is delay in left ventricular ejection and a corresponding late closure of the aortic valve (Fig. 14,*2,3*). In fact closure of the aortic valve occurs even later than closure of the pulmonary valve. The two components of the second sound then in left bundle branch block consist of first, the pulmonic valve closure and secondly, the aortic valve closure. During inspiration the second sound becomes single or more closely split. This is caused by the normal behavior of the pulmonary valve closure moving toward the late aortic component, thus narrowing or eliminating the split with inspiration. During expiration the splitting of the second sound widens because of the normal earlier appearance of the pulmonary closure. This behavior of the second sound with inspiratory narrowing has been referred to as *paradoxical splitting of the second* heart sound.[18, 19]

This so-called paradoxical splitting of

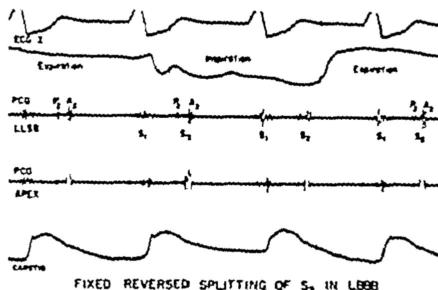


Fig. 12. [illegible] M.E. Phonocardiogram recorded during [illegible] with inspiration and [illegible] with expiration. [illegible] fixed reversed splitting of the second sound. The aortic [illegible] follows the pulmonic [illegible] 0.07 sec. both during inspiration and expiration. The patient [illegible] 8-year-old man with arteriosclerotic [illegible] hypertensive heart disease with left bundle branch block, congestive heart failure, and marked [illegible]. ECG I, Electrocardiogram, lead I. PCG, Phonocardiogram. LLSB, Left lower sternal border. S_1, First heart sound. S_2, Second heart sound. P_2, Pulmonic component of second heart sound. A_2, Aortic component of second heart sound.

the second heart sound has been well documented in complete left bundle branch block.[illegible] (Fig. 11).

Ferloff and Harvey[illegible] have described an interesting variation in the behavior of the second sound in cases of left bundle branch block with associated right heart failure. They found that these cases have a fixed splitting of the second sound rather than a paradoxical splitting (Fig. 12). The first component of the second sound in these cases is produced by closure of the pulmonary valve, and the second component by delayed closure of the aortic valve. However, with inspiration the failing right ventricle cannot increase its stroke output; therefore there is no appreciable movement of the pulmonic closure, and therefore no narrowing of the split during inspiration. These authors emphasize that in cases of left bundle branch block with congestive failure, clinical auscultation does not permit the distinction between left and right bundle branch block. However, the phonocardiogram does afford the distinction because the delayed aortic component is synchronous (allowing for mechanical delay) with the dicrotic notch of the simultaneously recorded carotid pulse.

Left bundle branch block, of course, is not the only cause of paradoxical splitting of the second sound. Other well recognized causes of this phenomenon include severe aortic stenosis, some cases of patent ductus with a large left-to-right shunt, and now, more recently, coronary artery disease with left ventricular dysfunction, some cases of hypertension, some cases of the Wolff-Parkinson-White syndrome, and certain cases of idiopathic hypertrophic subaortic stenosis.[illegible] Harvey[illegible] states that at times paradoxical splitting may be erroneously diagnosed because of the fact that with inspiration one component of the second heart sound may be masked or become fainter, giving the auditory impression of a single sound.

Paradoxical splitting of the second sound has been regarded as a highly characteristic finding in complete left bundle branch block. In fact, Gray[illegible] has emphasized that this paradoxical splitting is to be regarded as an essential clinical feature of left bundle branch block. At the same time, however, it should be noted that in some cases of

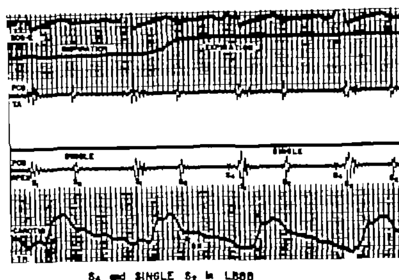


Fig. 13. Phonocardiogram in Patient T.H. with left bundle branch block. The second sound is single during both inspiration and expiration. During expiration a presystolic or atrial gallop (S_4) is evident; this is not seen during inspiration, which suggests that it may be a left ventricular phenomenon. *ECG-II*, Electrocardiogram—Lead II. *PCG*, Phonocardiogram. *TA*, Tricuspid area. *DN*, Dicrotic notch. S_1, First heart sound. S_2, Second heart sound (single). S_4, Presystolic or atrial gallop.

what is called complete left bundle branch block, lesser degrees of delay of the aortic component will cause the aortic closure to occur at essentially the same time as the pulmonic closure, resulting in either no splitting or a very closely split second sound[94, 9] (Fig. 13).

Levine and Harvey[94] have also emphasized that lesser degrees of left ventricular conduction delay, or so-called incomplete left bundle branch block, do not result in paradoxical splitting of the second sound. In these cases the splitting may be perfectly normal.[100]

VENTRICULAR GALLOP (THIRD HEART SOUND OR DIASTOLIC GALLOP). Diastolic gallop sounds are quite common with left bundle branch block.[91, 94] This may be because of the commonly associated underlying hypertensive, ischemic, valvular, or myocardial disease with congestive failure.

ATRIAL GALLOPS. Atrial or presystolic gallops are rather common in association with left bundle branch block (Fig. 13). The rather frequent occurrence of the presystolic gallop in left bundle branch block has most likely contributed to the illusion of a split first sound in left bundle branch block and may account for the frequent descriptions of splitting of the first sound in the older literature.[17, 101, 102] Associated systemic hypertension or prolongation of the P-R interval, in association with complete left bundle branch block, tends also to increase the frequency of occurrence of this sound.

Sequence of ventricular activation and ejection

Normal heart (*Fig. 14,1*). Braunwald, Fishman, and Cournand[104] have conclusively demonstrated in the normal individual that the onset of left ventricular contraction precedes the onset of right ventricular contraction by a brief interval (averaging 0.01 sec.) (Fig. 14,*1*). They also have shown that, although the left ventricle normally begins to contract before the right ventricle, its ejection commences later; that normally the left ventricular ejection ends before right ventricular ejection does; and that this normal asynchrony of right and left ventricular ejection is responsible for the normal splitting of the second heart sound, consisting first of the aortic component followed by the pulmonic component.

Left bundle branch block (*Fig. 14,2,3*). In 1935 Wolferth and Margolies[14] demonstrated a significant delay in the ejection

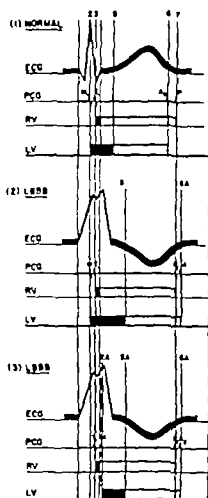


Fig. 14. Diagram of sequence of ventricular activation and ejection. (1) Normal (adapted from Braunwald, Fishman, and Cournand[188]). (2) Left bundle branch block (adapted from Braunwald and Morrow[187] and Bourassa, Boiteau, and Allenstein[189]). (3) Left bundle branch block (adapted from Gray[92]). *ECG*, Electrocardiogram. *PCG*, Phonocardiogram. *RV*, Right ventricle. *LV*, Left ventricle.

1, Onset of QRS. *2*, Onset of LV activation. *2.1*, Onset of LV activation (LBBB). *3*, Onset of RV activation. *4*, Onset of RV ejection. *5*, Onset of LV ejection (normal). *5.1*, Onset of LV ejection (LBBB). *6*, End of LV ejection (normal). *6.1*, End of LV ejection (LBBB). *7*, End of RV ejection. *3-4*, Isometric contraction of RV. *2-5*, Isometric contraction of LV (normal). *2-5.1*, Isometric contraction of LV (LBBB). *2.1-5.1*, Isometric contraction of LV (LBBB). *M*, Mitral component of first sound. *T*, Tricuspid component of first sound. *A_2*, Aortic component of second sound. *P_2*, Pulmonic component of second sound.

from the left ventricle in cases of complete left bundle branch block. These same workers also demonstrated that the closure of the aortic valve occurs later than closure of the pulmonary valve. They attributed their findings to asynchronism in the beginning of ejection from the two ventricles due to delay on the left side.

Gray[92] found with careful phonocardiographic studies that delay in closure of the aortic valve was due in all of his cases of complete left bundle branch block to delay in activation of the left ventricle and that delay in closure of the mitral valve was always found when the first heart sound could be analyzed and the onset of the carotid arterial pulse was correspondingly later. He concluded that the delay of the aortic component of the second heart sound was a delay that affected the whole of the left ventricular activity. Using simultaneous phonocardiographic recordings from the pulmonary and mitral areas, electrocardiogram, and indirect carotid pulse recordings, he concluded that there was a significant delay in mitral closure with the Q-M_1 interval averaging 0.11 sec. (normal, 0.06 sec.) and a delay in the onset of the carotid pulse from the Q wave to 0.16 sec. (normal, 0.09 sec.). He found no prolongation of left ventricular systole with an average of 0.30 sec., the same as that for right ventricular systole (Fig. 14,3).

In contrast with these findings were those of Braunwald and Morrow,[187] who studied 5 patients with complete left bundle branch block and performed simultaneous catheterizations of the right and left ventricles. In 4 of their cases the onset of left ventricular contraction either preceded or was simultaneous with the onset of right ventricular contraction. In 1 patient the onset of left ventricular contraction followed the onset of right ventricular contraction by 0.01 sec. They pointed out that the left bundle is a short broad band which divides near its origin into numerous fasciculi, some of which arise even proximal to the bifurcation of the bundle of His. They explained the absence of abnormal asynchronous ventricular contraction in cases showing the electrocardiographic picture of complete left bundle branch block by a conduction block in one of the

branches of the left main bundle or within the left ventricular myocardium. They believe that incomplete interruption of conduction can lead to the electrocardiographic configuration of complete left bundle branch block and can also account for the delay in the onset and termination of ventricular ejection. However, since they demonstrated in these cases that the onset of left ventricular contraction was essentially normal, they concluded that a considerable portion of the left ventricle in these cases must begin to contract at a normal time and must therefore be depolarized at a normal time.

Braunwald and Morrow[11] have observed that there is no consistent delay in the onset of left ventricular contraction, but that there is prolongation of left ventricular ejection in patients with the electrocardiographic configuration of complete left bundle branch block. They state that this correlates with the phonocardiographic observation of a single first heart sound but a paradoxically split second heart sound with a delayed aortic component in many of the patients with complete left bundle branch block. (Fig. 14,2)

Dickerson and Nelson[42] have commented that the frequency with which paradoxical splitting is found in left bundle branch block is strong evidence that mechanical delay must accompany electrical delay, and they believe that this tends to refute the experimental studies which did not show asynchronous ventricular contraction in left bundle branch block.[17]

Bourassa, Boiteau, and Allenstein[19] performed hemodynamic studies in a case of intermittent complete left bundle branch block. These workers found that the onset of left ventricular isometric contraction was not delayed with the occurrence of left bundle branch block, but that there was definite prolongation of the duration of left ventricular isometric contraction and proportional prolongation of isometric relaxation. Diastole is shorter than normal in left bundle branch block. Because of the prolonged isometric contraction, both the onset and termination of left ventricular systolic ejection were delayed in left bundle branch block, although the duration of left ventricular systolic ejection was no longer than when normal conduction was present. The delay in termination of systolic ejection from the left ventricle in left bundle branch block was thus found to be due to the delay in onset of systolic ejection. These workers concluded that prolonged isometric contraction of the left ventricle was probably responsible for the delayed closure of the aortic valve and paradoxical or fixed splitting of the second heart sound (Fig. 14,2)

Folli, Vitolo, Battioni, and Zocche[49] have studied the effect of experimental bundle branch block on mechanical systole and the relationship between mechanical and electrical systole in dogs. These workers recorded simultaneously intracardiac pressures and electrocardiograms in both ventricles before and after the production of left and right bundle branch block. Initially, in both ventricles the interval between electrical and mechanical events was 0.04 to 0.06 sec. After left bundle branch block this interval increased by 0.03 to 0.04 sec. (in one case there was no increase), making the delay between electrical and mechanical systole of the left ventricle 0.07 to 0.09 sec. Before the production of bundle branch block, isometric systole was found to begin simultaneously in both ventricles in all cases. After left bundle branch block was produced, the isometric contraction of the left ventricle began 0.02 to 0.05 sec. after that of the right ventricle. These workers concluded that in left bundle branch block the delay between electrical and mechanical events in the left ventricle increases and mechanical systole is increased and that the delay in mechanical systole of the blocked left ventricle is the same as the delay in the intrinsic deflection of the intracavitary electrocardiogram recorded from within the left ventricle. The interval between the electrical and the mechanical events in the right ventricle was unchanged in left bundle branch block.

In a recent very significant article, Morrow, Lambrew, and Braunwald[11] have published simultaneous records of pressures in the right ventricle and left ventricle in a patient with idiopathic hypertrophic subaortic stenosis who postoperatively developed complete left bundle branch block. They demonstrated that th[illegible] of contraction of the left ventricle

that of the right by 0.06 sec., a distinctly abnormal delay. These workers emphasized that the distinct delay in onset of left ventricular contraction in left bundle branch block provided hemodynamic confirmation that depolarization of the left ventricle occurred after that of the right.

Braunwald[10] has briefly summarized his observations on left bundle branch block. Since our paper in 1958 we have measured the time interval between the onset of the QRS and the onset of the pressure rise in the left ventricle in a number of other patients who showed the electrocardiographic configuration of complete left bundle branch block. Our more recent findings confirmed our older ones, namely, that these patients do not show a delay in the onset of the left ventricular pressure rise. On the other hand, the tracing which we published in 1964 is a surgically induced type of left bundle branch block which may well behave differently from the usual type associated with diffuse myocardial disease. Thus, at the present time it is my feeling that while the onset of the pressure rise in the left ventricle is usually not delayed in patients presenting with left bundle branch block, this may not always be the case, and in the only instance of surgically induced left bundle branch block which we have studied a definite delay in the onset of left ventricular contraction was observed.

Leatham[7] has recently stated that he believes that the onset of contraction of the left ventricle is seldom delayed in left bundle branch block. His conclusions are based on direct evidence in some of his own cases, as well as in the cases reported by Braunwald.[10,17] In support of this thesis, Leatham[7] points out as the fact that the first heart sound is seldom split in left bundle branch block, as would be expected if the onset of contraction of the right and left ventricles were asynchronous. He pointed out, in contrast, that in the case of a ventricular ectopic beat arising from the right ventricle (and thus of left bundle branch block pattern) there is wide and reversed splitting of the first sound, as would be expected.

Leatham[17] believes that left bundle branch block is usually really an arborization block. He pointed out that this fits the anatomy of the left bundle, which is very broad, with early spreading, so that it would be difficult for one lesion to completely interrupt the left bundle.

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Appraisal and reappraisal of cardiac therapy

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Antiarrhythmic drugs
Part VI. Clinical use of procaine amide

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In the previous article on the pharmacology of procaine amide it was noted that the major differences between quinidine and procaine amide in their action on cardiac tissue were quantitative rather than qualitative. Procaine amide has been used, therefore, in almost all situations in which quinidine has been indicated. In many cases it was tried only after quinidine had been unsuccessfully used, but several investigators have compared quinidine and procaine amide for the treatment of cardiac arrhythmias. It would appear from all the observations reported to date that procaine amide is an effective antiarrhythmic agent which may be used as an alternative drug to quinidine and occasionally as a supplementary agent. Where a parenteral or intravenous agent is required, procaine amide is frequently the drug of choice. The toxic effects of the two drugs upon cardiac tissue are qualitatively similar, although there are quantitative differences. Quinidine and procaine amide have different systemic toxic effects, which allows substitution of one agent for the other when required.

The relatively recent introduction of closed-chest controlled direct-current external cardiac depolarization for the reversion of cardiac arrhythmias to normal sinus rhythm has supplanted drug therapy in many institutions. There are many advantages to instantaneous reversion of cardiac arrhythmias, but the hazards of electrical countershock, the limitations of equipment, the difficulty in transporting patients or equipment, and the requirement for maintenance therapy with antiarrhythmic agents make the continued study of quinidine and procaine amide important.

Although it is customary in therapy to separate arrhythmias into those of supraventricular and those of ventricular origin, it is also important to know the duration of the arrhythmia and the clinical state of the patient. Procaine amide is successful in reverting chronic atrial arrhythmias (principally atrial fibrillation) in only about one fifth of the patients, but when it was used in a group with recent atrial fibrillation (of less than 2 weeks' duration), it caused reversion to normal sinus rhythm in about four fifths of the patients. Studies in patients with atrial flutter and atrial tachycardia of recent origin indicate that procaine amide is also an effective agent in these arrhythmias and may be used as an alternative drug to quinidine. In the management of extrasystoles of both atrial and ventricular origin, a number of reports indicate that procaine amide is effective. The dosage schedule used in the studies and management of atrial arrhythmias has varied widely because of variation in the requirements of the patients. With oral

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therapy single doses of 0.5 to 1.0 Gm every 3 to 4 hours have usually been successful but patients may respond to as little as 1 Gm per day or require as much as 10 to 12 Gm per day.

The treatment of ventricular tachycardia is usually considered to be an urgent and even an emergency procedure. The reasons for this attitude are based on the following facts: the arrhythmia usually develops in subjects with organic heart disease and particularly during the course of acute myocardial infarction; the development of ventricular fibrillation during ventricular tachycardia is not uncommon; and cardiac output falls dramatically at high ventricular rates. It should be noted, however, that subjects with ventricular tachycardia often tolerate this aberrant rhythm for weeks and months if the heart rate is not excessive and cardiac output remains adequate. There are many individual case reports of the successful management of patients with ventricular tachycardia with procaine amide. In most of these patients intravenous therapy was used, and there appears to be a distinct advantage in using procaine amide rather than quinidine for this form of administration. The greater effectiveness and lesser toxicity of procaine amide in comparison to quinidine has frequently been observed with intravenous therapy of ventricular tachycardia, and in about four fifths of the patients ventricular tachycardia can be successfully converted to supraventricular rhythm. The precautions during intravenous use include constant electrocardiographic monitoring and almost continuous reading of the blood pressure in order to observe the effects of the drug upon the rhythm and the circulation, since hypotension may occur during intravenous administration. The rate of administration should be about 50 to 75 mg. per minute and should not exceed 100 to 125 mg. per minute. The total dose required to revert ventricular tachycardia may be as high as 4 Gm. intravenously. Not infrequently, the hypotension that may exist because of the tachycardia itself is accentuated by intravenous procaine amide and a vasopressor agent may be required. The re-establishment of a supraventricular pacemaker is most often accompanied by restoration of the blood pressure toward previous values. The problem of hypotension is greatly reduced by intramuscular administration of procaine amide and rarely occurs with oral therapy. For this reason, the latter two routes are preferred over intravenous administration unless prompt therapy is urgently required.

The management of arrhythmias in patients who have received digitalis and in whom the arrhythmia may reflect digitalis intoxication in association with electrolyte depletion due to diuretic therapy deserves special attention. Paroxysmal atrial tachycardia with 2 to 1 atrioventricular block has been recognized as an arrhythmia frequently induced by the above-stated pathophysiologic state. It is apparent that electrical countershock is hazardous in these patients because of the development of cardiac standstill or uncontrollable ventricular fibrillation. In many institutions procaine amide in conjunction with potassium replenishment is considered to be the treatment of choice. But the controversy about the simultaneous use of procaine amide and digitalis, particularly when the latter drug has been given in excess, requires careful evaluation of each individual patient before a decision as to the appropriate therapeutic step is made. We have frequently successfully treated with procaine amide both ventricular tachycardia and ventricular premature systoles due to digitalis overdosage. We have also used procaine amide in the treatment of paroxysmal atrial tachycardia with 2 to 1 atrioventricular block, but this therapeutic regimen requires careful electrocardiographic surveillance because of the dangers inherent in giving antiarrhythmic agents in the presence of atrioventricular block. It is generally accepted that in the presence of complete heart block both quinidine and procaine amide are contraindicated and individuals who have had Stokes-Adams syncope should not be given these agents because of the greater sensitivity of the pacemaker tissue to these drugs even if the syncopal attack has been precipitated by ventricular tachycardia and ventricular fibrillation. These individuals are more properly managed with isoproterenol medication for acute phases and cardiac pacemakers for long term management.

The toxic manifestations of procaine amide may be divided into cardiac and noncardiac systems. The electrocardiogram is frequently altered, but the prolongation in the P-R, QRS, or Q-T intervals need not necessarily be regarded as a manifestation of toxicity but rather as manifestations of effects on cardiac muscle essential to the action of the drug. Some of these electrocardiographic abnormalities can be reversed by intravenous sodium lactate, presumably as a function of the sodium ion; whether sodium lactate will impair the therapeutic efficiency of procaine amide as an antiarrhythmic agent has not been established. The hypotension that appears during intravenous medication, and the decreased cardiac contractility observed in experimental animals and in anesthetized man during cardiac surgery, have already been referred to in this article. The use of vasopressor agents to counteract hypotension has been recommended by several investigators; careful control of the rate of administration of procaine amide may decrease the degree of hypotension.

During oral medication anorexia, nausea, and vomiting may occur, particularly with large doses of the drug. Agranulocytosis has occurred in a small number of patients during prolonged oral medication and routine blood counts and smears should be performed. The toxic reactions ascribed to procaine amide include chills and fever, drug rashes, generalized lymphadenopathy, arthralgias, muscle pains, and eosinophilia. Several reports have indicated that procaine amide may also produce the syndrome of systemic lupus erythematosus, including the L. E. cell, proteinuria, and serositis. In one patient these abnormalities disappeared after withdrawal of procaine amide; in another patient the abnormalities (except for an elevated sedimentation rate) were all suppressed by continuous steroid therapy administered for 1½ years, together with procaine amide, which was required to control this patient's recurrent ventricular tachycardia. Other unusual reactions to procaine amide may be reported as more patients are treated for long-term prophylaxis in the management of recurrent cardiac arrhythmias.

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tassium supplements given. When a more critical situation exists, the use of a chelating agent[21-24] or a β-adrenergic blocking agent[25,26] may rapidly counter the toxic effect of digitalis, and be life-saving.

There is little doubt that the elderly are more prone to toxic reactions than are young patients,[3-6,11,27,28] and the margin of safety between therapeutic and toxic doses becomes very fine. Not only are the elderly liable to the toxic effects already mentioned, and with a very high mortality when these occur,[29] but other less well-recognized toxic effects may occur. Mental confusion which may be severe and which may persist for some weeks after withdrawal of digitalis, has been reported,[30] although more commonly confusion and hallucination lasting about 48 hours occurs.[11,31,32]

Gynecomastia as a toxic effect of digitalis in elderly males was reported in 1953[33] and has been noted by others.[34] It disappears when treatment has ceased, but it is most important to exclude underlying bronchial carcinoma or cirrhosis of the liver before accepting this as a digitalis effect.

Even if we accept the fact that the use of ECG has increased the frequency with which digitalis intoxication is detected, it is quite clear that digoxin, which has largely replaced digitalis in common use, is not without danger and it may be that this change in prescribing habit may be responsible for the fact that gastrointestinal upset is less often seen as an early toxic effect, since the pure glycoside is less irritant than digitalis leaf.

Before placing the blame for the increasing frequency of toxic arrhythmias on the cardiac glycosides, we must take into account the advent over this period of the oral diuretic agents, most of which cause loss of potassium and thus enhance the effect of digitalis on the myocardium. It seems to be likely that a combination of the improved potency of digoxin over digitalis leaf and the widespread use of potassium-losing thiazide diuretics is the reason that the incidence of reported toxic effects from digoxin has climbed steadily from 4 per cent in 1959 to 21 per cent in 1964. Only by adequate use of potassium supplements, and an increased awareness of the many facets of toxicity especially among the elderly, will this trend be reversed.

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Notations in acid-base balance

An individual involved in the finer points of acid-base balance comes into contact with various biochemical notations. The lack of a standardized nomenclature has led to confusion, particularly for the student or those who have only casual contact with acid-base physiology. Part of the difficulty stems from the fact that acid-base physiology is the child of pure chemistry and clinical medicine. The notations used often reflect the orientation of the individual, and many terms and symbols have lost the more precise definitions given them by the pure sciences.

The Henderson-Hasselbalch relationship in its theoretical form deals with the activity of ions. Since activities or apparent concentrations are not practical to work with, a factor, the activity coefficient, is used to convert activity to concentration. The activity coefficient is related to the ratio of the activity of an ion to its concentration. The term in which the concentration is expressed determines which symbol is used for activity coefficient.

$$\gamma = \frac{a}{m}$$

where a equals activity and m equals molal concentration.

$$Y = \frac{a}{c}$$

where c equals molar concentration and

$$f = \frac{a}{N}$$

where *N* equals the mole fraction.

The most frequently seen notation for activity coefficient is γ but, strictly speaking, Y is more appropriate, since molar concentrations are most commonly used in acid-base work. A notable exception is the NBS buffer standards which are based on a molal scale.

Another source of confusion is found in the expression of the bicarbonate fraction of the Henderson-Hasselbalch equation. In the full derived equation, the numerator represents a molar concentration. This is so because the true dissociation constant K has been divided by the activity coefficient to yield a new constant K'.

$$[H+] = K\frac{H_2CO_3}{a_{HCO_3}}$$

$$a_{HCO_3} = Y \cdot c_{HCO_3}$$

$$[H+] = \frac{K}{Y} \cdot \frac{H_2CO_3}{c_{HCO_3}}$$

$$K/Y = K'$$

$$[H+] = K'\frac{H_2CO_3}{c_{HCO_3}}$$

or

$$pH = pK' + Log\frac{c_{HCO_3}}{H_2CO_3}$$

The bicarbonate concentration may be written $[HCO_3]$, c_{HCO_3}, or $[BHCO_3]$. Various authorities object to either one or the other notations.* $[HCO_3]$ is the most confusing since some authors consider this to be "bicarbonate concentration," whereas others use it to mean "apparent bicarbonate concentration (activity)." c_{HCO_3} is a little cumbersome although its meaning is clearer. $[BHCO_3]$ is frowned upon presumably because the presence of the "B" suggests that cations are bases. Few thinking investigators suffer from this illusion in this day and age and accept "B" as a general symbol for cation. This notation has the advantage of simplicity and even without the brackets leaves little doubt that the quantity is expressed in terms of concentration rather than activity. However, it tends to conceal the fact that the Henderson-Hasselbalch relationship deals with ionic concentrations or activities. If reference is made to the activity of

*Bicarbonate activity.
†Bicarbonate concentration.

bicarbonate, αaco₂ is the clearest notation and [HCO] the most ambiguous one

Since the time of Boh α has been used to indicate the solubility coefficient or milliliters of gas dissolved in 1 ml. of plasma (.510 for CO_2 in plasma at 38°C.). Van Slyke and associates also defined α in Bohr terms in the late twenties nd made reference to the quantity α/76 22.26 or α 0591 which when multiplied by pCO gives H_2CO_3 (dissolved CO plus true carbonic acid). This factor which may be expressed by H_2CO (mM./L.) /pCO (mm.Hg) (.0301 for CO_2 in plasma t 38°C.), was not assigned a specific designation until Severinghaus introduced the notation "S" or solubility factor and made a clear distinction between α and S

Despite the fact that α s definition as milliliters of gas per milliliter of solution be temporal preference several modern thors substitute α or lower case a, the Anglicized corruption of α, for the solubility or "S" factor If current usage dictates a redefinition of α or any other notation, then no objection can be offered "A foolish consistency may be the "hobgoblin of little minds, but undisciplined inconsistency is the hobgoblin of scientific minds. We should take a lesson from the pulmonary physiologist and hematologist who have made great strides in standardizing their notations nd terminology A standard set of notations would benefit the seasoned clinician and in estigator as well as the student of acid-base physiology

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Electrocardiographic changes induced by phenothiazine drugs

During the past years there have been communications n the medical literature in regard to electrocardiographic changes during the administration of thioridazine -⁴ The purpose of our study published i the *Canadian Medical Association Journal* was t reveal whether these changes are real, whether they are characteristic of thioridazine and whether they occur with other phenothiazine drugs as well. If they do occur are they more frequently present w th the administration of thioridazine

To answer our questions we designed study in which thioridazine chlorpromazine, and trifluoperazine were administered to 6 ps hiatric patients in increasing dosages (thioridazine and chlorpromazine 200 to 1,200 mg and trifluoperazine 8 to 64 mg daily). The study followed Latin square design. Prior to each trial and twice during each drug period, ECG was recorded, levels of potassium and sodium in the blood were determ ned nd blood pressure and pulse were checked

Our findings confirmed that, in h ma beings, thioridazine produces a prolongation of the Q-T interval and modifies the terminal portion of the ECG e., the S-T segment and T and U w es The changes consisted of blu ting nd notching of the T w ves. The notching in some cases produced a double-bump appearance in which a T wav of reduced voltage formed the proximal bump and a positive U wa of increased voltage formed the distal bump. The changes were found to be not specific for thioridazine, since they occurred in 3 subjects who were taking chlorpromazine and in 1 subject taking trifluoperazine. Thioridazine in duced changes in all 6 subjects. On the basis of these findings, we assume that phenothiazine drugs ma ha e an effect on the ECG in human beings, nd that this effect resembles manifestations seen w th the administration of quinidine. This effect is most pronounced with thioridazine less so w th hlorpromazine, and least with trifluoperazine

Since the conclusion of this double-blind controlled experiment, electrocardiograms were recorded on 114 chronically psychotic patients who had been

Letters to the Editor

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To the Editor

In their paper "Ventricular Fibrillation, a Late Complication of Direct-Current Countershock," which appeared in the June, 1965 issue of the JOURNAL, Rothfeld and associates dismiss the possible role of digitalis in producing the ventricular fibrillation since the patient had taken this drug "with impunity prior to the procedure." It is known that countershock may unmask latent digitalis toxicity. It is for this reason that Lown originally advocated discontinuing digitalis for 24 hours before countershock is carried out and the more recent tendency is to withhold digitalis for longer periods before this procedure. In discussing his paper on the subject at the American Heart Association meeting last year Dreifus advocated a 2 week digitalis-free interval.

According to the protocol, the patient reported by Rothfeld and associates received her regular dose of digitalis leaf on the morning on which the countershock was carried out. After the first unsuccessful shock, multifocal premature ventricular systoles appeared, which are highly suggestive of digitalis toxicity. It would seem reasonable to conclude that the subsequent development of ventricular tachycardia and fibrillation hours after the countershock was greatly facilitated by the digitalis.

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To the Editor

Thank you for allowing us to reply to the comment made by Dr Wolfson regarding our report, Ventricular Fibrillation, Late Complication of Direct-Current Countershock.

In the cases described by Rabbino and associates, ventricular fibrillation occurred after attempted cardioversion of atrial tachycardia with block, an arrhythmia that followed rapid intravenous digitalization and almost certainly represented digitalis toxicity. We cannot agree with Dr Wolfson that a patient who has taken 100 mg of digitalis leaf daily for at least 6 months with no untoward effects represents an example of "latent digitalis toxicity." We might point out that there are at least two other reports of the occurrence of ventricular fibrillation after cardioversion in the absence of digitalis excess.

A recent paper by Corwin and associates is of interest in that it describes successful cardioversion of paroxysmal atrial tachycardia with block due to digitalis toxicity.

The purpose of our case report was not to discredit the important contribution of cardioversion to the treatment of arrhythmias, but rather to describe an important delayed complication of the procedure and to emphasize the need for observation in the postconversion period. Admittedly the precise pathogenesis of the ventricular fibrillation in our case is unknown but perhaps this report will stimulate further investigation into the effect of direct-current countershock on the fibrillation threshold of the heart.

A recent editorial[5] summarized current thinking: "The complications associated with direct-current precordial shock should in no way stigmatize this method as a dangerous procedure rather they bring into sharp focus the importance of judicious selection of patients for elective cardioversion, including precise electrocardiographic analysis of the ectopic mechanism technical perfection in the administration of the shock and the exhibition of extreme caution in the presence of excessive antiarrhythmic drug therapy. Identification of the risks and hazards prior to conversion should prevent many possible catastrophies."

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Les Sutures de l'Aorte Thoracique. Étude Clinique et Expérimentale. By Fernand Lantin M.D. Brussels, 1963, Editions Arscia, 171 pages.

This book, published in French in 1963, presents clinical observations and experimental studies of complications, particularly mycotic aneurysm and rupture of the suture line after operation on the thoracic aorta.

The importance of the anatomic distribution of the vasa vasorum in the aorta is emphasized. The incidence of mycotic aneurysm or rupture is shown to be directly proportional to the degree of resection of the adventitia from the aortic wall or its traumatization by vascular clamps.

Experimentally, the incidence of this complication after resection of the adventitia using sterile or unsterile sutures to close aortotomies was about 10 per cent. No complications were observed if the adventitia was left intact.

Because the incidence of complications is greater in the ascending aorta than in the descending aorta, the following was proposed as the possible etiology: (1) Resection of the adventitia from the ascending aorta removes more vasa vasorum than from elsewhere in the aorta, because of the location of the origin and anatomic distribution of these vessels. (2) The ascending aorta is subjected to more dynamic pressure and tension than is the descending aorta.

Guided by experimental results and clinical experience, particularly that of Professor Bram, of Leiden, the author makes the following conclusions: (1) The adventitia must be left intact if vascular complications are to be prevented. (2) Necrosis of the media develops around the stitches of the anastomoses. It is of importance, therefore, that the sutures be placed sufficiently far apart and not too close to the margin of the incision. (3) A longitudinal anastomosis in the ascending aorta is best overseen with double sutures. (4) After an operation involving aortic anastomoses, the symptoms that suggest mycotic aneurysm are fever, recurrent arterial embolism, and manifestations of sepsis. A secondary operation to remove infected material must be considered.

The Doctor as a Witness. Edited by William J. Curran, LL.M., S.M.Hyg., Director, Law-Medicine Institute, Boston University, Boston, Mass. Second edition. Philadelphia, 1965, W. B. Saunders Company, 196 pages. Price $5.75.

This small book should interest all physicians. It is clearly written and defines some of the important problems which confront the physician in court. Among the subjects discussed are preparation for trial, what makes a good medical witness, privileges and obligations of the doctor witness, opinion evidence and expert testimony, direct and cross-examination, compensation, and others. This useful book is recommended to all physicians and students of medicine.

Congenital Heart Disease. Correlation of Pathologic Anatomy and Angiocardiography. Volumes I and II. Edited by Jesse E. Edwards, M.D., Lewis S. Carey, M.D., Henry N. Neufeld, M.D., and Richard G. Lester, M.D. Philadelphia, 1965, W. B. Saunders Company, 890 pages. Price $45 per set.

These two volumes by Edwards and his coauthors are essentially an atlas of excellent illustrations and legends supported by a brief text. Diagrams are used to explain lesions and the associated hemodynamic disturbances. Roentgenograms, angiocardiograms, and photomicrograms are illustrated freely. Dr. Edwards and his associates have been interested for many years in the clinical pathology of patients with congenital heart disease, and these two volumes summarize very well their concepts and studies. Even though these books are more of the nature of a reference work and atlas, they should be made readily available to internists, cardiologists, pathologists, cardiac surgeons, and medical students. The average student and physician will find these volumes to be of great value as a reference work. The brief clinical data presented with the cases increase the value of the books for training purposes in clinical cardiology.

A Primer of Cardiac Catheterization. By Ross C. Kory, Theofilos J. Tsagaris, and Rodrigo A. Bustamente. Springfield, Ill., 1965, Charles C Thomas, 114 pages. Price $7.50.

This slim volume was evolved by the authors as a result of experiences in teaching cardiac catheterization to medical students, interns, and residents. The book is well designed to serve as an aid in the instruction of physicians-in-training with regard to commonly used cardiac diagnostic laboratory methods and their interpretation. The text is illustrated with 74 roentgenograms and intracardiac pressure recordings or diagrams, which are, with few exceptions, clear and well chosen. The bibliography is selective rather than exhaustive but certainly adequate for the intended audience. In addition to a discussion of cardiac and great-vessel pressure recordings, there is a presentation of methods of cardiac-output measurement, indicator-dilution curves, angiocardiography, and the use of the hydrogen electrode, dye curves, and inhaled foreign gases in the detection of right-to-left and left-to-right shunts. The reviewer has successfully employed an earlier version of this material in the introductory training of postgraduate fellows in cardiology. This volume is recommended as an aid in the instruction of medical student and house staff. Since it does not discuss indications, applications, or limitations of these diagnostic tests, it should not be employed without supplemental instruction. Because of the intentionally restricted treatment of the topic, the book will not appeal to most physicians in practice.

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Editorial

On teaching cardiology

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"There is much vulgar enthusiasm and too little recognition of the deeper meaning of the remark that the verb to teach is not a transitive verb.

Alan Gregg

I have been asked to comment on the teaching of cardiology. It may well be that appropriate discharge of the assignment is, for one of my conditioning, impossible. One does not teach cardiology—not to medical student, to house officer, to clinical fellow, nor to practicing physician. At most and best, one arranges certain factors in the environment of these students of several ages and categories, hoping thereby to permit them more readily to learn something about cardiology. In the end, most of what they come to know they will learn from patients: what patients tell them, observations made on patients, results of diagnostic studies performed on patients, response of patients to therapeutic efforts thoughtfully conceived and skillfully initiated by the physician, but tested in the end only by the patient himself and expressed in his responses to that treatment.

The pace at which the individual student's learning proceeds will be determined by the nature and degree of his personal projection into this relationship with his patients: the enthusiasm, persistence, and empathy with which he interrogates the patient about his illness; his formulation of historical data into sensible diagnostic possibilities; his pursuit of these possibilities through deliberately and discerningly oriented series of diagnostic studies—physical, physiological, and biochemical—not one thing done haphazardly and pointlessly, not one thing omitted from carelessness or lack of imaginative perception of the possible rewards of its pursuit.

The essence of the astute clinician has been identified as the capacity to make an intelligent guess; an alternative phrasing might present this "guess" as a closely reasoned judgment which avows that struggle for additional and decisive data is futile, and that the time has come to establish a therapeutic hypothesis to be tested in the highly personalized setting of the individual patient and his illness.

This latter decision can be made at ultimate best only if in the process of reaching it the student has sought out facts relevant to the specific diagnostic problem in the usual sources of stored information: textbooks, journals, lectures, conferences, and consultations with senior colleagues. To ignore these sources would indeed be folly, but to seek cardiologic competence by their zealous pursuit, to the ill judged compromise of time devoted to the study and care of patients them

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selves fosters weakness and dependency. The knowledge that comes from experience leads to skill, the knowledge that comes from words leads to erudition. A new recruit rarely has much medical skill and I think never can have too much. But of erudition there can be a surfeit.

To see, to ask, to know, to think, to feel, ultimately to be: only by being good cardiologists can we contribute determinatively to the evolving character and professional competence of those who would be our successors. With Alan Gregg we would acknowledge the imperative in pedagogy for writing and speaking clearly and vigorously, but would conclude with him also that "Much of our knowledge in medicine is still so incomplete that it does not offer the ideal material for a finished lecture, and in too slick presentation of a subject curiosity may suffer euthanasia while veracity is decorously but nonetheless thoroughly murdered." Why not assume that a teacher leads mainly by his example and that like pathologists we can more readily recognize the result than define the process.[3]

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Clinical communications

Significance of ventricular and pseudoventricular arrhythmias appearing after D.C. countershock

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Electrical countershock is a well-established effective method for terminating cardiac arrhythmias.[1] Transthoracic alternating current was first employed by Zoll and co-workers[1] for the treatment of ventricular fibrillation in man. Later it was used for terminating other arrhythmias as well. During the last 4 years, direct current has been successfully employed by Lown and co-workers in the treatment of various disorders of rhythm. The latter author has suggested that direct-current (D.C.) is superior to alternating-current (A.C.) countershock because of the greater margin of safety and efficacy of the former.[1]

Evaluation of a method of treatment can be made only after the information gained with extensive use is collected properly and then analyzed. Since the use of controlled electricity in terminating arrhythmias is rapidly becoming more widespread, it is obvious that a thorough knowledge of the indications, precautions, and complications is imperative. In other publications we have been interested in the arrhythmias appearing after D.C. countershock.[1] These have been mainly supraventricular. Significant ventricular ectopic rhythms related to A.C. shock are known to occur.[1] As more experience has been gained, other arrhythmias of ventricular origin have been reported after D.C. countershock as well.[1] Thus, it appeared that both types of current are capable of inducing arrhythmias. Hence, it seemed appropriate to study the incidence and mechanisms of production of ventricular arrhythmias (excluding extrasystoles) appearing immediately after D.C. countershock. Special care was taken to differentiate ectopic ventricular contractions from aberrant conduction of supraventricular impulses.

Material and methods

D.C. countershock was employed for the purpose of abolishing 310 episodes of arrhythmias (excluding ventricular fibrillation) in 207 patients. The types of heart disease in the order of their frequency were atherosclerotic heart disease, 111 patients; rheumatic heart disease, 87 patients; congenital heart disease, 4 patients; primary myocardial disease, 5 patients. The ages ranged from 17 to 86 years. The

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number of episodes and the type of arrhythmia are given in Table I. All patients had cardiac enlargement and showed some degree of heart failure at the time of the procedure. Digitalis had been administered in the majority of the patients. On 41 occasions the patients had received 1.2 Gm. or more of quinidine sulfate on the day of attempted conversion. Patients suspected of having digitalis intoxication, hypokalemia, or marked changes in repolarization due to quinidine were excluded from the present series. Seven hundred and thirty-one synchronized D.C. countershocks were administered by means of the Cardioverter.* The structure and function of this instrument, as well as the necessary precautions for its use, have been described by Lown and associates.[4,7] Synchronization was tested in every case by observing the moment of shock either on the oscilloscope screen or on a recording electrocardiographic paper. The energies employed are presented in Table II. Anesthesia with sodium methohexital† as reported previously[11] was used in the majority of the episodes. The energies used in patients converted electively without anesthesia were never greater than 100 watt-seconds. The paddles were located on the anterior surface of the thorax in 279 episodes. In the other 31 episodes an anteroposterior position was employed. The effects of the electrical shocks were observed on the oscilloscope screen, while a permanent graph was recorded (Standard Lead II or Chest Lead V_1). Continuous monitoring was performed for a minimum of 15 minutes after the procedure. Rhythm strips and/or complete electrocardiograms were obtained before countershock in all instances.

The first cycle preceding the widened QRS complexes which occasionally appeared after D.C. current could not be seen because of the brief period of stylus overshooting which followed the countershock. Therefore the diagnosis of aberrant ventricular conduction of supraventricular impulses was made whenever (1) there were instances of true aberration diagnosed by conventional criteria[12] in the control tracings of patients with flutter or fibrillation with irregular A-V responses which disappeared after a regular sinoatrial mechanism had been achieved and (2) the last R-R cycle in the paroxysm was not the longest.[14] In these instances the average ventricular rate was generally above 150 per minute. On the other hand, the diagnosis of true ventricular rhythms was made whenever (1) the widened QRS complexes appeared immediately after countershock in patients displaying only ordinary extrasystoles[11] in control tracings, (2) the paroxysms were initially rapid, the rate then decreasing progressively until its extinction (Munk-Gaskell phenomenon)[16] and (3) fusion beats were present.[17] The

Table I. Arrhythmias treated with D.C. countershock

Arrhythmia	Number of patients	Number of episodes	Abolishment of arrhythmias (%)
Atrial fibrillation	118	131	90
Atrial flutter	49	60	100
Ventricular tachycardia	32	4	100
Ventricular flutter	2	65	100
Nodal tachycardia	5	5	20
Sinus tachycardia	1	1	0
Total	207	310	

*Erroneously interpreted as atrial flutter with 2:1 A-V conduction.

Table II. Energies employed in D.C. countershock treatment of diverse arrhythmias

Watt seconds	Times employed
50	4
75	8
100	313
150	199
200	120
300	62
400	25
Total	731

*American Optical Company, Chelsea, Mass.

†Brevital.

average ventricular rate ranged between 70 and 130 in cases with rapid idioventricular beats, and was over 140 in instances of ventricular tachycardia.[18]

Results

"Rapid idioventricular" beats transiently followed countershock on seven occasions in 5 patients (Table III, Figs. 1 and 2). The first three beats of the paroxysm in Case 1 were considered to be "ventricular tachycardia" because of a rate of 150 per minute.[18] The number of beats in each run ranged from 4 to 23, although the exact number could not be determined with accuracy because of the brief period after countershock during which a perfect trace cannot be obtained.

All of the paroxysms showed a definite structure characterized by an initial faster rate, generally under 120 per minute, which declined progressively until its disappearance (Munk-Gaskell phenomenon).[16] The energies with which they appeared were 300 watt-seconds, four times, and 400 watt-seconds, three times. The preshock arrhythmias were atrial fibrillation on five occasions, and atrial tachycardia and atrial flutter on one occasion each. The original arrhythmias were terminated in 6 patients, yet two episodes occurring in 1 patient (Case 4) were not abolished even with energies of 400 watt-seconds. The duration of the episodes was seen to increase with higher wattages in 2 patients (Fig. 2). Three subjects in this group had been premedicated with 1.2 Gm. of quinidine on the day on which conversion was attempted. In all patients displaying a rapid idioventricular rate, preshock and postshock electrocardiograms showed premature ventricular contractions. The number of the latter did not seem to increase after the return of sinus rhythm.

Table III. Ventricular and pseudoventricular arrhythmias occurring after D.C. countershock

Patient	Pre-existing arrhythmias	Energy of shock	Rate	Number of ectopic beats	MG phenomenon	Energies of previous shocks	Result	Quinidine premedication
				Ventricular				
1	AT	300	150–111	4	Yes	100–150–200	SR	No
2	AF	300	112–100	9	Yes	100–150–200	SR	No
3	AF	400	115–94	7	Yes	100–150–200–300	SR	Yes
4	AF	300	106–77	11	Yes	100–150–200	Failure	Yes
4	AF	400	100–70	23	Yes	100–150–200–300	Failure	Yes
5	AF	300	100 —	4	Yes	100–150–200	SR	No
5	AF	400	111–86	8	Yes	100–150–200–300	SR	No
6	VF	150	150–75	30	Yes	100 (29 times)	†	No
6	VF	150	140–80	22	Yes	100 (29 times) + 150	†	No
6	VF	150	130–75	19	Yes	100 (29 times) + 150 (2 times)	†	No
6	VF	150	150–100	17	Yes	100 (29 times) + 150 (3 times)	†	No
				Pseudoventricular				
7	AF	100	150–188	6	No	—	Failure	Yes
8	AF	100	150–200	9	No	—	Failure	Yes
9	AF	100	150–91	14	No	—	Failure	Yes

*Watt-seconds.
†Reversed [illegible] high-degree A-V block.
AT, Atrial tachycardia; AF, Atrial fibrillation; [illegible] Atrial flutter; VF, Ventricular fibrillation; MG, Munk-Gaskell [illegible]

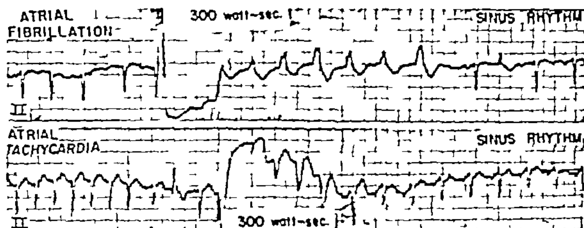


Fig. 1. [illegible] appearing after [illegible] treatment of atrial fibrillation (upper strip). [illegible] the lower strip. Note that [illegible] the [illegible] progressive [illegible] extinction (Munk-Gaskell phenomenon).

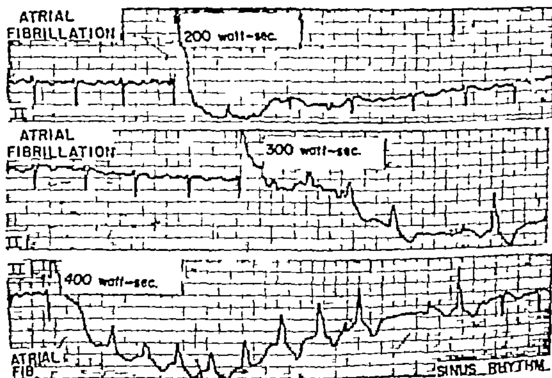


Fig. 2. Idioventricular beating appearing after D.C. countershock. Note that the number of ectopic contractions is directly proportional to the energy employed. Only one idioventricular beat is seen after 200 watt-seconds, but four and eight ectopic contractions are seen after 300 and 400 watt-seconds, respectively.

All patients had received three to four countershocks before the appearance of the arrhythmia.

Three patients in the present series showed runs of aberrant intraventricular conduction simulating ventricular paroxysmal tachycardia (Table I Fig 3) At first glance, the arrhythmia seemed to have been induced by the countershock, but closer analysis showed that sinus rhythm had not been re-established and that the postcountershock electrocardiogram was similar to the control one, which also displayed aberrant beats. Aberration of the right bundle branch block type was seen in 3 patients, but a left bundle branch block morphology was also seen in 2 of them. On one occasion there were some abnormal beats intermediate in contour which were not fusion beats, but rather the result of this simultaneous functional bilateral bundle branch block.[14] The aberrant paroxysms whose rate ranged from 150 to 188 per minute did not manifest the Munk-Gaskell arrangement since the last R R cycle was not necessarily the longest They were not observed after a regular sinoatrial mechanism was established

There was one instance of ventricular fibrillation which occurred after D C countershock (Fig 4) The patient was a 47 year-old man with atherosclerotic heart disease and ventricular tachycardia (rate of 212 per minute) in whom conversion was attempted with an energy of 75 watt seconds. The test shock had been previously observed on the oscilloscope screen and was considered to be properly synchronized outside the vulnerable zone. When actually delivered to the patient (upper strip of Fig 4) it was seen to fall approximately 0 15 second after the beginning of the QRS

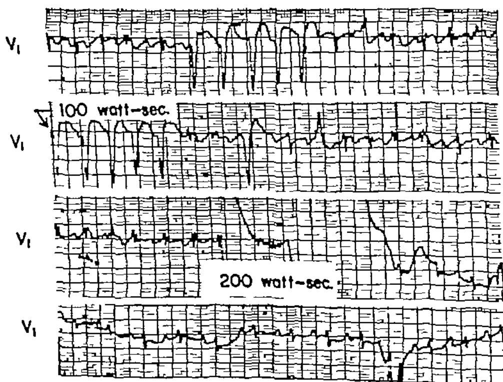


Fig 3. Atrial flutter with aberrant ventricular conduction imitating ventricular paroxysmal tachycardia appearing after the administration of quinidine. The widened QRS complexes displaying the morphology of both right and left bundle branch block were seen prior to, as well as after an unsuccessful attempt to revert the arrhythmia Aberration disappeared immediately after sinus rhythm returned. The first abnormal beat in the upper strip is preceded by a long R R cycle (rule of aberration[14]). The paroxysm did not show a Munk-Gaskell type of arrangement.

Fig. 4. Ventricular fibrillation produced by an improperly synchronized shock in a patient with ventricular tachycardia (upper strip). The iatrogenic arrhythmia subsided spontaneously (middle strip). The bottom strip shows sinus rhythm after properly synchronized D.C. countershock.

complex in Lead V and apparently during early repolarization. Ventricular fibrillation ensued after this countershock, lasted for 61 seconds and promptly reverted to ventricular tachycardia with a rate similar to but with a morphology different from the initial one. Five minutes later a second attempt at conversion was made. The test shock was seen to fall 0.08 second after the beginning of the QRS complex in Lead V. The difference in the synchronized timing was related to a change in electronic sensing from a negative to a positive deflection of the QRS complex. This second shock was followed by prompt restoration of sinus rhythm.

One patient with high-degree A-V block received 39 D.C. countershocks for the treatment of a similar number of episodes of ventricular flutter. The incidence of conversion to the basic rhythm was 100 per cent. However, after the twenty-ninth shock energies of 100 watt-seconds which had been previously used to terminate the arrhythmia became ineffective and energies of 150 watt-seconds had to be employed. These energies abolished the arrhythmia but consistently resulted in a slow ventricular tachycardia which spontaneously decreased in rate (from 150 to 75 per minute) until its disappearance (Fig. 5). The thirty-third shock was delivered after one of the monitoring electrodes of the Cardioverter had accidentally fallen off the chest. This immediately led to the appearance of multiple oscillations on the oscilloscope which were erroneously attributed to ventricular fibrillation. Two minutes later inspection of the simultaneously obtained electrocardiogram revealed the true nature of events. The shock had thus been applied during a period of A-V block and not during ventricular fibrillation (Fig. 6). A run of ventricular tachycardia appeared after this unnecessary countershock and was similar to other paroxysms seen in this patient. Thereafter the energy output was set at 125 watt-seconds and six other runs of ventricular flutter were abolished with immediate return to sinus rhythm.

Comments

The postshock incidence of severe ventricular arrhythmias in this series (0.008 per cent, 6/731) is similar to that of Lown

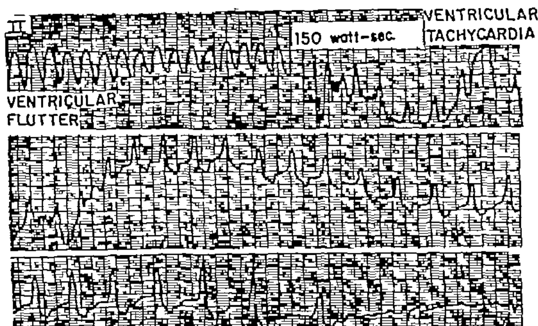


Fig. 5. Ventricular "tachycardia" appearing after countershock treatment of ventricular flutter. The rate of the paroxysm is initially rapid, thereafter decreasing progressively until its extinction (Munk-Gaskell phenomenon). Second-degree A V block is seen toward the end of the lower strip.

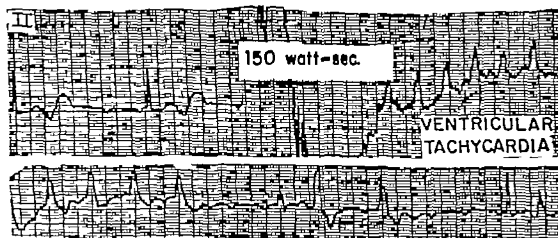


Fig. 4. Iatrogenic ventricular tachycardia produced in a patient with second-degree A V block and paroxysmal ventricular flutter (same patient as in Fig. 5). D.C. countershock was improperly applied when one of the recording electrodes during the defibrillation had fallen off the chest, thereby producing a false image of ventricular fibrillation on the oscilloscope screen.

(0.005 per cent 3,600). There was only one case of ventricular fibrillation in 731 instances of synchronized D.C. counter shocks applied to 207 patients. An analysis of this iatrogenic arrhythmia revealed that synchronization was relatively late. When the shock was timed closer to the beginning of the QRS complex, ventricular fibrillation did not occur even though the same energy outputs were used.

It is well established that the accuracy of synchronization should be determined b

fore countershock.[8] For impulses falling in the vulnerable phase are known to produce ventricular fibrillation.[18] Prior to the occurrence of ventricular fibrillation, timing of the test impulse was made simply on the oscilloscope. Subsequently, and because of this event, the synchronized beat stimulus was recorded on the direct electrocardiogram. Only after adequate synchronization is assured should the shock be applied to the patient. In the average case of atrial fibrillation with a moderate ventricular response, visual observation may suffice. However, in the case of tachycardias with widened QRS complexes an error in synchronization may occur if only the transient trace on the oscilloscope is observed. In these cases the shock should be timed so as to occur as close as possible to the beginning of the QRS complex. For instance, in the case presented in Fig. 4, the electrical stimulus apparently fell near the very beginning of repolarization, an area usually considered to be "safe" when one is dealing with slower ventricular rates. The possibility that in rapid ventricular rates the vulnerable phase is shifted closer to the QRS complexes should be considered. In addition, when wider ventricular deflections occur, partial repolarization may have begun prior to the completion of the QRS complex. In this patient the most important conclusion which can be drawn was that ventricular fibrillation did not recur when the shock was delivered closer to the beginning of the QRS complex.

Observation of the occurrence of rapid idioventricular beating after use of the method under consideration seems worth commenting on. If the patient with ventricular flutter is excluded, only one of the other episodes could be classified properly as ventricular tachycardia according to Bellet's criteria, that occurring in one patient with a rate exceeding 130 per minute for a few beats.[11] In all cases the arrhythmias disappeared spontaneously without requiring additional treatment.

The paroxysms were believed to represent ectopic impulse formation, and their appearance after an electrical shock following a brief interval of asystole, as well as their initial faster rate with progressive slowing and disappearance, resemble certain simple, long known electrophysiologic facts. As far back as 1878, Munk[19] observed that after the application of the second ligature of Stannius a single mechanical stimulus in the frog's heart elicited a series of beats which were at first rapid but which later became progressively slower. Several years later, Gaskell[17] showed that this rhythm originated in the A-V funnel. This particular type of ectopic beating was designated by Scherf as the *Munk-Gaskell phenomenon*.[16]

Since the transient irregular ventricular contractions appeared after countershocks of high intensities, and since they seemed to be energy-dependent (their number increasing with higher intensities), the question was raised whether they were due to a direct effect of D.C. countershock on the myocardium.

In this respect, of interest is the patient in whom sudden electrode maladjustment caused the application of an unnecessary countershock (150 watt-seconds) which in turn induced ventricular tachycardia. This iatrogenic arrhythmia helped to clarify the mechanism of three similar paroxysms which occurred after 29 countershocks had been given to a patient with 29 episodes of ventricular flutter. It had not been very clear whether the ventricular tachycardia had been an intermediate arrhythmia manifesting itself after electrical depolarization and before establishment of the basic rhythm. Intermediate supraventricular rhythms are rather frequent after countershock treatment of atrial flutter and fibrillation. In previous communications they were interpreted as either being spontaneous manifestations of diseased atria or representing a direct action of countershock on the heart muscle.[12]

However, the mode of appearance of the postcountershock ventricular arrhythmias, as well as the character of their relationships (Munk-Gaskell phenomenon), suggested that they were electrically induced. Therefore, it seems that in the patient with ventricular flutter both effects of D.C. countershock were manifested with energies of 150 watt-seconds: therapeutic (disappearance of ventricular flutter) and toxic (iatrogenic ventricular tachycardia). With this assumption in mind, we reduced the energy of the following shocks to 125

watt-seconds, which was found to be effective in abolishing ventricular flutter without recurrence of the iatrogenic arrhythmia.

A review of the literature on ventricular arrhythmias induced after D.C. countershock reveals that they fit two patterns. The first pattern, as in the cases presented in this communication, appears in the electrocardiogram as soon as a reproducible tracing becomes clear. In turn, these arrhythmias either can be a manifestation of improper synchronization, as the cases reported by Morris[17] and by Killip[22] (Fig. 4) or can appear in spite of adequate synchronization. In the latter category falls the second episode of Killip's case[22] (Fig. 5) and Lown's patient with atrial fibrillation of 22 years' duration.[4]

In addition, there is a second type of true ventricular arrhythmia which appears from several seconds to several hours after countershock has established sinus rhythm, the significance of which is not clear.[11-23] The possibility that these arrhythmias might represent toxic effects of quinidine[11] or digitalis[23-21] exposed and perhaps enhanced by countershock has been suggested.[11]

Lown and co-workers have emphasized the relative safety of D.C. over A.C. countershock. A smaller incidence of ventricular fibrillation and myocardial damage in the dog was found with D.C. than with A.C. current.[1] Ventricular fibrillation developed in 2 out of 8 patients treated by Zoll and associates[2] with alternating current in one series, and 4 times in a larger series of 227 episodes.[32] On the other hand, no instance of ventricular arrhythmia was seen in the series of Jouve and associates[33] who used alternating current in the treatment of 22 episodes of diverse dysrhythmias. These authors, however, recognized that with the instrumentation employed by them it was impossible to record tracings during actual conversion, so that a considerable number of short-lived intermediate rhythms could well have been overlooked.

After extensive studies, Lown and associates developed a modified capacitor or D.C. discharge which was safe and effective in defibrillating the heart.[19] This underdamped impulse, 2.5 msec. in duration and released from a 16 microfarad capacitor through a 100 mh. inductance, did not produce ventricular fibrillation when delivered outside the refractory phase.

In our department, we have confirmed the absence of ventricular fibrillation and cardiac arrest[17,34] when the Cardioverter is used to deliver multiple high-energy shocks to dogs.[34] Yet, multifocal ventricular extrasystoles, ventricular tachycardia, A-V block, and intraventricular block have been observed after multiple shocks of 400 watt-seconds. Therefore, it seems that, even after a properly synchronized shock, arrhythmias can occur in the experimental animal. These findings agree with the work of Zak and Peleška, who reported that under special conditions the heart can show either functional or morphologic damage.[35] Peleška demonstrated two types of ventricular fibrillation in dogs, using various ranges of voltages, wattages, and pure condenser discharges.[36] One type appeared when lower voltages or lower energies were used, and defibrillation could be effected easily. The other type occurred after the application of high voltages and high energies, and these arrhythmias tended to be irreversible. When an inductance was connected in series with the condenser, the discharges did not elicit ventricular fibrillation unless they fell within the vulnerable phase.[35]

Two severe types of ventricular arrhythmias are seen in Fig. 6, obtained from an experiment in a dog. Ventricular fibrillation triggered by a countershock of 0.75 watt-seconds that fell within the vulnerable phase was easily reverted by a second countershock. On the contrary, a D.C. impulse of 400 watt-seconds that fell within the "safe" zone induced multifocal ventricular activity which was not converted to sinus rhythm by means of an additional countershock. It should be re-emphasized that with the instrument employed in the study reported in this communication ventricular fibrillation is rarely produced unless many high-energy shocks are delivered to the animal's heart.[34]

Hence, the findings in the experimental animal somewhat resemble the events occurring in man. As in the dog, energy-dependent ventricular fibrillation did not occur in 730 instances of properly sync-

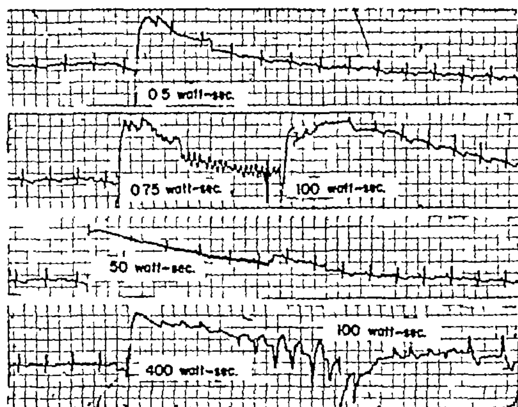


Fig. 7. Dog experiment I illustrating the two types of severe ventricular arrhythmias seen after the use of the Cardioverter. The upper strip shows that there is no response to a shock of low intensity (below the fibrillation threshold) even if it falls in the vulnerable phase. Ventricular fibrillation appears in the second strip after a shock of slightly above threshold values is delivered during the vulnerable phase. This low-energy ventricular fibrillation was easily reverted by an additional countershock. In the third strip a shock delivered with an intensity several times [illegible] threshold produces no response even though it falls in the vulnerable phase. Finally, the lower strip illustrates multifocal ventricular tachycardia appearing after shocks of high intensities falling outside the vulnerable phase.

nized D.C. shock. Two points deserve mention. First, it is improbable that the relationship between the size and weight of the animal on the one hand and the wattage employed on the other hand can be duplicated in human beings (small children excluded). Second, the iatrogenic arrhythmias that occurred in the present series disappeared spontaneously. Moreover, reversion of the arrhythmia has been easily effected by means of additional countershocks in instances of ventricular fibrillation reported by other authors.[21,24] Clinical experience thus confirms that ventricular arrhythmias related directly and exclusively to D.C. countershock (appearing immediately after the procedure) have posed no problem for the patient. These toxic, transient effects of electrical current are similar to the ones produced by mechanical irritation.[47,?] It seems that transient injury produced by either method and manifested either by increased rhythmicity or S-T segment elevation[49] promptly disappears because of the sealing off of the injured cells by the formation of a new membrane.[51,44]

The differentiation between paroxysms of rapid idioventricular beating and runs of aberration of supraventricular impulses was easily made by taking into consideration the information stressed in previous sections of this communication. This distinction is of more than academic importance, for it should make the physician decide whether additional electricity should be administered to the patient or whether the procedure should be put off until another time. Aberrant ventricular phenomenon is not so rare in rapid supraven

tricular arrhythmias and the 3 cases presented here represent instances in which this phenomenon could have been interpreted as having been induced by therapeutic electrical current.

Summary

D.C. countershock is an effective method for terminating cardiac arrhythmias. Seven hundred and thirty-one synchronized electrical discharges were employed for the purpose of abolishing 310 episodes of diverse arrhythmias in 207 patients. There was only one episode of ventricular fibrillation in the present series. It was attributed to improper synchronization. Iatrogenic ventricular tachycardia was observed five times in 2 patients. Rapid idioventricular beats occurred on six occasions. The induced ventricular paroxysms were initially rapid with the rate declining progressively until its extinction (Munk-Gaskell phenomenon). All iatrogenic arrhythmias were short lived and disappeared spontaneously. They were easily differentiated from aberration of supraventricular impulses.

Ventricular arrhythmias related to D.C. countershock can be manifested immediately after the procedure, as well as from a few seconds to hours after electrical conversion to sinus rhythm. The former group may either result as a consequence of improper synchronization or represent a direct effect of countershock on the myocardium. These toxic effects appear to be transient and have posed no threat to the life of the patients in our series or in other similar cases reported in the literature. The relationship between electrical depolarization of the heart and ventricular arrhythmias appearing after the return of sinus rhythm is not clear although some of these paroxysms seem to have a significant connection with quinidine or digitalis premedication.

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Paradoxical splitting of the second heart sound in the Wolff-Parkinson-White syndrome

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In the Wolff-Parkinson-White (WPW) syndrome a portion of ventricular myocardium is depolarized prematurely. Whether mechanical prematurity also occurs and gives rise to abnormal ventricular asynchrony has been debated.[1-4] Since certain mechanical events related to right and left ventricular systole generate the first and second heart sounds, changes in the normal sequence of ventricular systole might be expected to result in changes in timing of the heart sounds. Evidence of abnormal ventricular asynchrony was found in 3 of 4 patients with the pre-excitation syndrome.

Methods

Phonocardiograms were recorded on an Electronics for Medicine DR8 research recorder. Recordings were made at the high right and high left sternal borders, the low left sternal border, and the apex. A Sanborn pneumograph belt attached to a Statham P23Db transducer was used to record respirations. Indirect carotid arterial pulse recordings were made with a bell stethoscope head attached to a Statham P23Db transducer. Paper speed was 100 mm. per second, and time lines were 0.02 second apart. Twelve lead electrocardiograms were recorded on each patient.

Case reports

Case 1. A. W. This 13-year-old boy had been well except for bouts of tachycardia. Physical examination was unremarkable, except for a Grade 2 (of 6) ejection type systolic murmur at the high left sternal border and wide, fixed splitting of the second heart sound. Chest roentgenograms were normal. A twelve-lead electrocardiogram showed pre-excitation (Fig. 1, Table I).

A bradycardia with a rather marked sinus arrhythmia was apparent. Escape beats and occasional runs of an escape rhythm at a rate of 55 per minute were present. These escape beats had a right bundle branch block configuration and were thought to be of A-V nodal origin. Frequent fusion beats were present.

Phonocardiography (Fig. 2) demonstrated a soft systolic murmur at the high left sternal border. Beats with pre-excitation showed wide paradoxical splitting of the second heart sound (Fig. 2,A). The carotid arterial pulse tracing showed that closure of the aortic valve followed closure of the pulmonic valve. The splitting narrowed slightly during inspiration.

During pre-excitation the first heart sound began 110 msec. after the onset of the delta wave and 20 msec. after the onset of the QRS proper (Fig. 2,A). With fusion beats the first heart sound began 60 msec. after the onset of the QRS (beat 2 in Fig. 2,B). A prominent fourth heart sound was demonstrable. Nodal escape beats also showed wide split

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Table I. Summary of electrocardiographic findings

Case	Total QRS duration (sec.)	Delta wave (sec.)	P-R interval (sec.)	Frontal plane axis: QRS (degrees)	Frontal plane axis: Delta wave (degrees)	Delta wave in Lead V1
V.W.	0.14	0.09	0.11	0	−40	Diphasic
R.S.	0.10	0.05	0.09	0	−15	Diphasic
R.O.	0.12	0.06	0.08	−60	−30	Diphasic
C.H.	[illegible]	0.06	0.10	−30	0	Diphasic

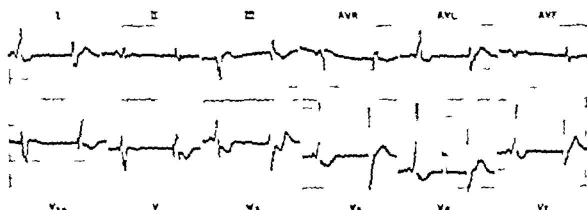


Fig. 1. Case 1. Electrocardiogram showing pre-excitation.

ting of the second heart sound, but here the pulmonic closure followed rather than preceded aortic. Beats showing variable degrees of fusion also showed variable splitting of the second heart sound. Fusion beats which had a prominent delta wave showed narrow but paradoxical splitting of the second heart sound. With greater degrees of fusion a single second heart sound occurred, and with even greater degrees of fusion the delta wave disappeared and splitting became "normal" (beat 2 in Fig. 2,B).

A right heart catheterization was carried out. Oxygen saturations, pressures, and position of the tricuspid valve were normal. A tachycardia with wide, bizarre QRS complexes occurred but stopped spontaneously several hours later.

At the present time attacks of paroxysmal tachycardia are infrequent and are adequately controlled by the performance of a Müller maneuver.

Case 2. R.S. This 14½-year-old boy had no cardiovascular symptoms. An episode of supraventricular tachycardia at the age of 1 month had precipitated congestive heart failure, but tachycardia had never recurred. Except for a Grade 2 systolic murmur at the high left sternal border and paradoxical splitting of the second heart sound, physical examination was normal. Posteroanterior and lateral chest roentgenograms were normal. An electrocardiogram showed pre-excitation (Fig. 3, Table I). A phonocardiogram (Fig. 4) demonstrated splitting of the second heart sound, with slight widening of the split during expiration. A simultaneous carotid arterial pulse showed that closure of the aortic valve followed closure of the pulmonic valve. The first heart sound followed the onset of the delta wave by 80 msec. and the onset of the QRS proper by 30 msec.

Case 3. R.O. Except for episodes of paroxysmal tachycardia this 15-year-old boy had no symptoms. No murmur was present but there was paradoxical splitting of the second heart sound. Chest roentgenograms were normal. An electrocardiogram showed pre-excitation (Fig. 5, Table I). Phonocardiography (Fig. 6) demonstrated splitting of the second heart sound with widening of the split during expiration. A simultaneous indirect carotid arterial pulse tracing was of poor quality, but the dicrotic notch appeared to closely follow the second component of the split. The variation in the splitting was due primarily to changes in timing of the first component of the second heart sound. The first heart sound followed the onset of the delta wave by 90 msec. and the onset of the QRS proper by 30 msec. The duration of the delta wave was difficult

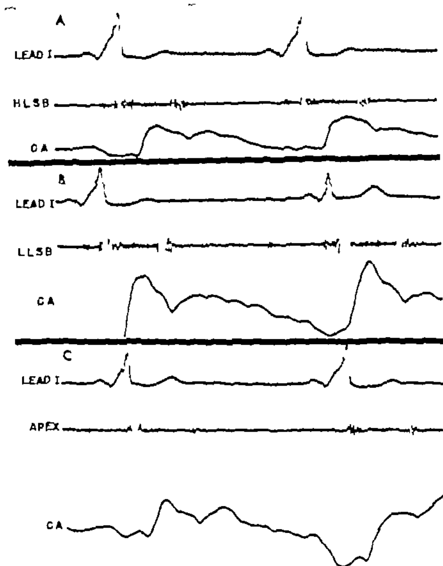


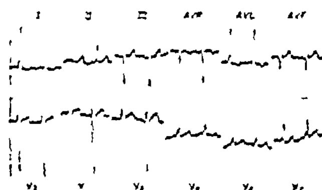
Fig. 2. Case 1. Simultaneous ECG, phonocardiogram, and indirect carotid arterial pulse tracing. *A*, Phonocardiogram at the high left sternal border shows paradoxical splitting of S_2. *B*, Phonocardiogram at low left sternal border. The first beat shows pre-excitation and S_1 begins 20 msec. after the onset of the R wave. The second beat is a fusion beat and S_1 begins 60 msec. after the start of the R wave. *C*, Phonocardiogram recorded at the Apex. S_1 is louder with the first beat, which shows slight fusion.

to inverse in Lead I but in other leads it was 0.06 second in duration.

Case 4. C. H. H. Bouts of supraventricular tachycardia had been the only symptom in this 13-year-old boy. The second sound was not audibly split and no murmur was present. Posteroanterior and lateral chest roentgenogram were normal. An electrocardiogram showed pre-excitation (Fig. 7, Table I). Phonocardiography (Fig. 8) demonstrated very narrow splitting of the second heart sound during inspiration and a single heart sound during expiration. The simultaneously recorded indirect carotid arterial pulse tracing showed that the first component of the second sound was aortic closure. The first heart sound followed the onset of the delta wave by 110 msec. and the onset of the QRS proper by 60 msec.

Results

In none of the 4 patients was there evidence of associated heart disease. All had experienced at least one attack of



F g 3 Case Elect nt gr hm pres t t n

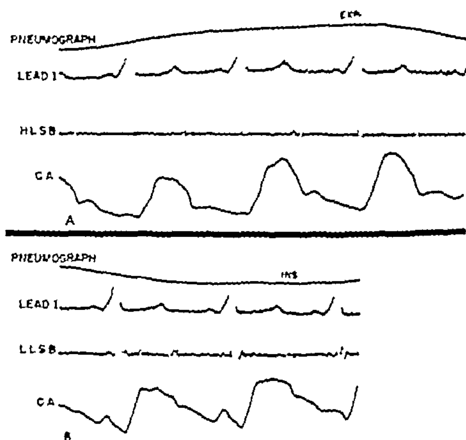


Fig. 4 Case 2. *A*. Phonocardiogram recorded at the high left sternal border shows paradoxical splitting of S_1 with slight widening of the split during expiration. *B*. At the lower left sternal border S_1 begins 30 msec. after the onset of the R wave.

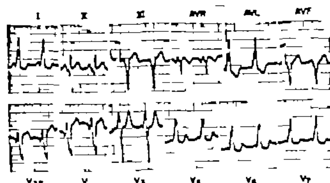


Fig 5 Case 3 Electrocardiogram showing pre-excitation.



Fig. 6 Case 3 Phonocardiogram t the high left sternal border shows splitting of S_2 during expiration and single S_2 during inspiration.

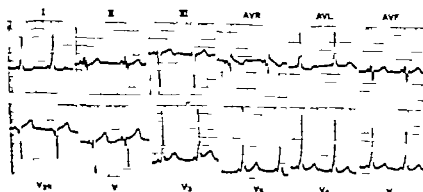


Fig 7 Case 4 Electrocardiogram showing pre-excitation.

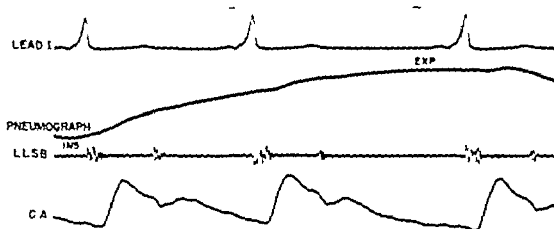


Fig. 8. Case 4. Phonocardiogram at the low left sternal border shows narrow splitting of S2 during inspiration and single S2 during expiration (normal).

praventricular tachycardia. Electrocardiograms in each case were quite similar. Each showed a prominent *delta* wave and the frontal plane axes of the delta wave and QRS proper were similar, always showing left axis deviation and always being within 30 degrees of each other. In the horizontal plane the QRS vector was directed to the left and posteriorly, resulting in a deep S wave in Leads V_1 and V_2 and a tall R wave in Leads V_5 and V_6. The delta wave was diphasic in Lead V_1 and upright in the left precordial leads in all.

In 3 of the 4 patients *paradoxical splitting of the second heart sound occurred* when pre-excitation was present. Simultaneously recorded carotid arterial pulse tracings showed that the second component shortly preceded the dicrotic notch and thus represented aortic closure. In 2 patients the splitting was present throughout the respiratory cycle but narrowed slightly with inspiration. In the same 3 patients the first heart sound began 20 to 30 msec. after the onset of the QRS proper.

Discussion

Since its original description as a clinical entity in 1930,[7] the WPW syndrome has attracted much attention and excited considerable controversy. The electrocardiographic diagnosis of the syndrome depends on the presence of a short P-R interval and prolonged QRS. Both features result from the presence of a delta wave, a slurred initial portion of the QRS which results from early depolarization of a portion of ventricular myocardium. The presence of mechanical prematurity in the involved ventricle has been debated. Ferrer and associates concluded from a study of the relationship of the onset of the QRS to the onset of the rise in pressure in the right ventricle and in the brachial artery that mechanical systole was delayed in both ventricles. It must be noted, however, that this delay was relative to the delta wave and not to the QRS proper. Dick and associates[2] were unable to document abnormal ventricular asynchrony using electrokymography of aortic and pulmonary artery motion. Another study[4] utilized roentgenkymography and purported to show precontracting areas in the ventricles. The persistence of these precontracting areas after normal conduction had replaced pre-excitation raises doubts as to their significance. The phonocardiographic studies of March, Selzer, and Hultgren[6] demonstrated paradoxical splitting of the second sound in 1 patient and no evidence of ventricular asynchrony in several others.

Contraction normally begins first in the left ventricle and mitral closure slightly precedes tricuspid. Ejection normally terminates first in the left ventricle, and aortic closure precedes pulmonic.[8,9] Abnormal ventricular asynchrony should produce changes in the timing of the components of the first and second heart sounds. If the

mechanical prematurity involved the right ventricle, tricuspid and pulmonic closure might precede mitral and aortic closure respectively. If mechanical prematurity involved the left ventricle an abnormally widely split S_1 and S_2 might occur.

Normally the interval between the onset of left ventricular electrical systole and the first heart sound is about 55 msec.[1] In Cases 1, 2 and 3 the first heart sound began 80 to 110 msec. after the onset of the delta wave but only 20 to 30 msec. after the onset of the R wave. The onset of the R wave was assumed to be at the point of abrupt change in slope at the terminus of the delta wave. The R wave was presumed to represent left ventricular electrical systole. It seems to be unlikely, therefore, that mitral closure was responsible for the earliest portion of the first heart sound. The arrhythmia present in Case 1 offered further evidence of early closure of the tricuspid valve during pre-excitation. In several fusion beats (beat 2 in Fig. 2,*B*) the left and right ventricular depolarizations were probably nearly simultaneous, and the first heart sound began 60 msec. after the onset of the R wave. In the beats showing typical pre-excitation (beat 1 in Fig. 2,*B*) the R-S_1 interval was only 20 msec. and mitral closure presumably occurred long after the first sound began.

All 3 of these cases demonstrated paradoxical splitting of the second heart sound. There was, therefore, evidence that contraction began and ejection ended first in the right ventricle. It could be argued that this abnormal ventricular asynchrony was due not to premature right ventricular events but to delayed left ventricular contraction. Indeed, the degree of left axis deviation seen in our patients is not often seen in healthy children and suggests some alteration in depolarization of the left ventricle. Grant and associates have stated that some alteration in the electrical axis is present during pre-excitation in 50 per cent of the cases. They thought, however, that this was due to early activation of either the superior or inferior division of the left bundle and not to delay in left ventricular activation. Even with block of the superior division from other causes, there is little or no QRS prolongation.[12] With complete left bundle branch block there is paradoxical splitting of the second heart sound but no splitting of the first heart sound.[13,14] It seems, therefore, that prematurity of right ventricular events better explains the ventricular asynchrony.

In some of the fusion beats the QRS was only 0.04 second long and consisted solely of an R wave in Lead I (beat 2 in Fig. 2,*B*). Right ventricular and left ventricular electrical systoles must have been nearly simultaneous, and right ventricular depolarization was completely masked. When right ventricular depolarization began before or ended after left ventricular depolarization, it was quite evident, either as a delta wave during pre-excitation or as a broad S wave with right bundle branch block.

Probably all 4 cases here reported are Type B as initially classified by Rosenbaum and associates.[15] Their classification depended on the form of the delta wave and QRS proper in the right precordial and esophageal leads and divided pre-excitation into Types A and B. Type A electrocardiograms were those with dominant R waves and upright delta waves in the right precordial leads. Type B electrocardiograms all had dominant S waves in the right precordial leads, and in Case 5 presented as a typical Type B, the delta wave was diphasic in Lead V_1. Our experience supports the contention of Hecht[6] and Latour and Peuch[17] that pre-excitation involves the right ventricle in Type B.

Summary

In 3 of 4 cases of Type B WPW syndrome, right ventricular mechanical events were premature, the first portion of the first heart sound represented tricuspid closure and there was paradoxical splitting of the second heart sound. All 4 children were healthy except for episodes of supraventricular tachycardia. Cardiac catheterization was carried out in 1 patient and nothing abnormal was found.

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Ventricular repolarization in congenital aortic stenosis

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The severity of congenital aortic stenosis has been difficult to estimate using clinical criteria. Although the scalar electrocardiogram is useful in predicting the severity of pulmonary stenosis,[1] it is not nearly so helpful in predicting the severity of congenital aortic stenosis. This difficulty probably results from the fact that valid electrocardiographic criteria for left ventricular hypertrophy in both adults and children have been difficult to establish. This study was undertaken to define useful criteria for assessing the severity of congenital aortic stenosis in children from the scalar electrocardiogram.

Materials and methods

The electrocardiograms of 63 children with congenital valvular aortic stenosis or discrete subvalvular aortic stenosis who were seen at The Hospital for Sick Children, Toronto, were studied in detail. The electrocardiograms were recorded by a direct writer Sanborn Viso-Cardiette with a paper speed of 25 mm. per second and a standardization of 1 millivolt = 10 mm., except in certain instances of high voltage when the standardization was set at 1 millivolt = 5 mm. The peak systolic gradient across the stenosis was measured at rest in each case by retrograde left heart catheterization. Patients were not anesthetized but were sedated with a mixture of Demerol, Largactil, and Phenergan as described by Smith and associates.[2] The age at the time of catheterization varied from 11 months to 15 years, with a mean of 9 years and 11 months. No one was receiving digitalis at the time of the study.

The peak systolic gradient was correlated with certain measurements of the scalar electrocardiogram. The depth of the S wave in Precordial Leads V_1 and V_4 and the height of the R wave in precordial Leads V_4 and V_6 were measured directly from the electrocardiogram in millimeters. The mean axis of the QRS complex in the frontal plane was determined using the "null contour" method of Grant[3] (i.e., the mean axis is at right angles to the standard or unipolar lead with an equiphasic or transitional QRS complex where the algebraic sum of all deflections above the base line (+) and those below the base line (−) is close to zero) and the standard hexaxial frontal reference frame[4] (Fig. 1). The mean frontal axis of the T wave was determined in a similar manner. In the horizontal plane the mean axis of the QRS complex and the T wave was determined using Grant's "null contour" method[3] in a quantitative way, as recommended by Lamb,[5] using the horizon

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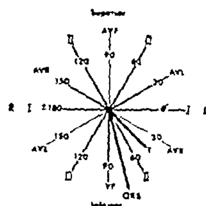


Fig. 1. Frontal reference frame (adapted from Massie and Walsh) showing the position of the normal mean QRS and T wave axes.

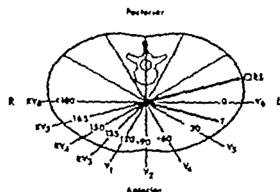


Fig. 2. Horizontal reference frame (adapted from Massie and Walsh) showing the position of the normal mean QRS and T-wave axes.

tal reference frame of Massie and Walsh (Fig. 2). Here the mean axis is at right angles to the precordial lead with the equiphasic or flat QRS or T wave. Angular direction of a mean vector can be estimated to within 15 degrees of accuracy using this technique. The QRS-T angle in the frontal or horizontal plane is assumed to be a positive quantity regardless of the position of the QRS and T wave vectors. For instance, if the frontal projection of the QRS mean vector is +75 degrees, and the frontal projection of the T wave vector is −30 degrees, the QRS-T angle in the frontal plane is 105 degrees, not 45 degrees. The R/T ratio as described by Sokolow and Lyon[6] was measured in Precordial Leads V_1 and V_6. The spatial QRS-T angle was calculated from the mean axis of QRS and T in the frontal and horizontal planes in the reference frames of Figs. 1 and 2 altered to fit Helm's notation and using his tables.[7] The results were analyzed statistically by dividing the cases into two groups: those with gradients across the aortic valve above and below 50 mm Hg, using the chi-square test of Fisher modified for small series. Throughout the study, cases in which the mean frontal axis of QRS was less than +45 degrees were separated from those in which the mean frontal QRS angle was greater than 45 degrees. Since cases with a frontal axis of QRS less than +45 degrees were inconsistent, they were eliminated and only the 49 cases with a frontal axis of QRS greater than +45 degrees were analyzed statistically.

Results

In the total group of 65 cases of congenital aortic stenosis, 49 had a mean frontal axis of QRS of +45 degrees or greater and this group was analyzed in detail. In 75

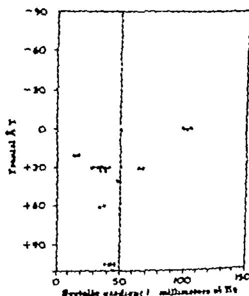


Fig. 3. The frontal mean axis of the T wave is more superior when the systolic gradient across the aortic valve is greater. Only one case with a vertical frontal QRS axis has a frontal mean T-wave axis above 15 degrees.

of these cases the systolic gradients were under 50 mm Hg and in 24 cases the gradients were over 50 mm Hg

Voltage In the right precordial leads the S wave in Lead V_1 was greater than 25 mm in 2 cases in which the systolic gradients were less than 50 mm Hg and was greater than 25 mm in only 6 cases in which the systolic gradients were over 50 mm Hg (X^2 = 1 476 and $p < 30$)

The S wave in Lead V_2 was greater than 35 mm in 3 cases in which the systolic gradients were less than 50 mm Hg and was greater than 35 mm in only 6 cases in which the gradients were over 50 mm. Hg (X^2 = 1 1444 and $p < 30$)

Measurement of the voltages in left precordial leads showed an R wave over 30 mm in Lead V_6 in 10 cases in which the systolic gradients were under 50 mm Hg and in 11 cases in which the systolic gradients were over 50 mm (X^2 = 0 014 and $p < 95$)

The R wave in Lead V_6 was over 25 mm in 6 cases in which the systolic gradients were less than 50 mm Hg and in only 4 cases in which the gradients were less than 50 mm Hg (X^2 = 0 076 and $p < 90$)

None of these measurements of voltage is reliable for separating cases of mild aortic stenosis from those of severe aortic stenosis.

Repolarization The mean frontal axis of the T wave was superior to +15 degrees in only 1 case in which the systolic gradient was less than 50 mm Hg but was superior to +15 degrees in 16 cases in which the systolic gradients were over 50 mm Hg (X^2 = 18 496 and $p < 001$) The relationship of the frontal axis of the T wave to the systolic gradient is shown in Fig 3

Serial electrocardiograms in one case are

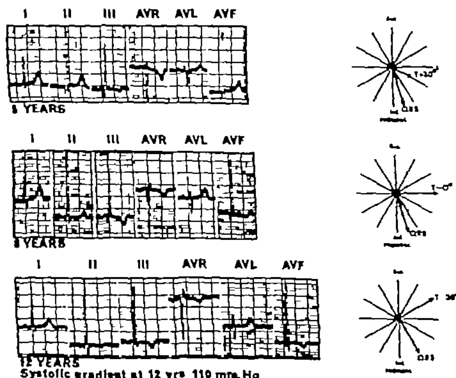


Fig 4 The scalar electrocardiogram taken at 5 years, 8 years and 12 years in the same patient. The frontal axis of the T wave becomes more superior with growth, thus widening the QRS-T angle At 12 years of age, the systolic gradient was 110 mm. Hg

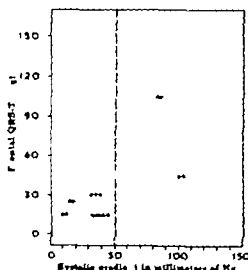
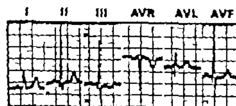


Fig. 5. The frontal QRS-T angle is narrow in cases with small systolic gradients across the aortic valve. In only 2 cases with a vertical QRS axis is the frontal QRS-T angle greater than 60 degrees when the gradient is small.



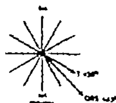


Fig. 6. The scalar electrocardiogram from a case with a very small systolic gradient. The mean frontal T wave axis is +30 degrees, and the frontal QRS-T angle is only 15 degrees.

illustrated in Fig. 4. These show a progressive elevation of frontal T wave axis with growth in a child whose systolic gradient at 12 years of age was 110 mm. Hg.

The frontal QRS-T angle was greater than 60 degrees in only 2 cases in which the systolic gradients were less than 50 mm. and was greater than 60 degrees in 9 cases in which the gradients were over 50 mm. Hg ($X^2 = 4.539$ and $p < .05$). The relationship of frontal QRS-T angle to systolic gradient is shown in Fig. 5. Case R.S. shown in Fig. 6 had tall R waves in Standard Lead II and III and aV$_F$ suggesting left ventricular hypertrophy, yet had a frontal T wave axis of +30 degrees and a frontal QRS-T angle of only 15 degrees. The relationship of T waves to QRS indicates a small systolic gradient across the aortic valve and this was found to be only 11 mm. Hg at the time of left heart catheterization.

Examination of the T waves and QRS in precordial leads revealed interesting results. In no case in which the systolic gradient was less than 50 mm. Hg was the axis of the T wave anterior to +45 degrees, but in 6 cases in which the gradients were over 50 mm. Hg the horizontal T wave axis was *anterior to +45 degrees* ($X^2 = 5.559$ and $p < .02$).

The horizontal QRS-T angle estimated from the precordial leads using the method and reference frame previously outlined under *Methods* was greater than 60 degrees in only 1 case in which the systolic gradient was less *than 50 mm. Hg and was greater* than 60 degrees in 7 cases in which the gradients were greater than 50 mm. Hg ($X^2 = 4.183$ and $p < .05$). Fig. 7 demonstrates the relationship of the horizontal QRS-T angle to the systolic gradient across the aortic valve.

Case R.S. shows a deep S wave in Leads V_1 and V_2 and a very tall R wave in Leads V_5 and V_6 (Fig. 8) indicating left ventricular hypetrophy by the usual criteria and suggesting a severe gradient across the aortic valve. The horizontal QRS-T angle is only 15 degrees, and the horizontal axis of the T wave is −15 degrees, indicating a small gradient which was subsequently found at the time of left heart catheterization.

The frontal QRS-T angle and the hori-

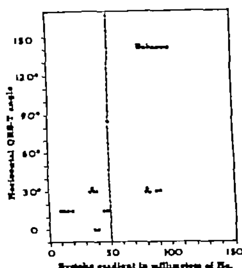
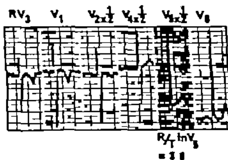


Fig. 7 The horizontal QRS-T angle is narrow in cases with small systolic gradients across the aortic valve. Only one case with a small gradient across the aortic valve and a vertical frontal QRS axis has an angle greater than 60 degrees.



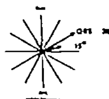


Fig. 8 The precordial scalar leads from the same patient as shown in Fig. 6. Despite voltage of 39 in Lead V and 58 in Lead V, the systolic gradient across the aortic valve is only 11 mm. Hg. The horizontal QRS-T angle is 15 degrees, and the R/T ratio in Lead V is just 3.8.

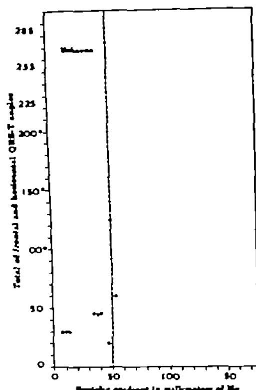


Fig. 9 The total frontal and horizontal QRS-T angle is normally less than 100 degrees in patients with a small systolic gradient across the aortic ... who have a vertical frontal QRS axis.

zontal QRS-T angle were added together and this total QRS-T angle was related to the systolic gradient across the aortic valve in Fig. 9. Only 2 cases with a total QRS-T angle over 100 degrees have gradients of less than 50 mm. Hg, whereas 11 cases with a total QRS-T angle over 100 degrees have a gradient greater than 50 mm. Hg (X^2 = 8.213 and p < .01).

A more accurate way of relating the frontal QRS-T angle to the horizontal QRS-T angle is the calculation of the spatial QRS-T angle. Using Helm's tables,[7] it was found that in only 2 cases in which the systolic gradient was less than 50 mm. Hg was the spatial QRS-T angle over 60 degrees, whereas in 13 cases in which the gradients were greater than 50 mm. Hg the spatial QRS-T angles were over 60 degrees (X^2 = 10.115 and p < .01).

The ratio of R over T was then calculated in Precordial Lead V. This ratio did

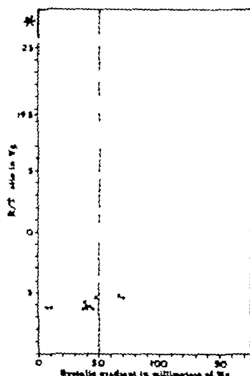


Fig. 10. The R/T ratio in Lead V_6 is always less than 10 in cases with a small systolic gradient across the aortic valve and if the frontal QRS axis is vertical T waves flat or negative in these 3 cases.

not exceed 10 in any case in which the systolic gradient was under 50 mm. Hg but it exceeded 10 in 10 cases in which the gradients were over 50 mm. Hg (X^2 = 10.601 and p < .01). The relationship of the R/T ratio in Lead V_6 to the systolic gradient across the aortic valve is shown in Fig. 10.

The R over T ratio in Precordial Lead V_6 shows a similar pattern. In only 2 cases does the ratio exceed 10 when the systolic gradient across the aortic valve is less than 50 mm. but it exceeds 10 in 12 of 24 cases in which the gradient is greater than 50 mm. Hg (X^2 = 8.589 and p < .02).

A study was made of serial changes in the scalar electrocardiograms of the 47 children in this group who had been followed over a period of time. In one child 11 electrocardiograms recorded at various ages were analyzed, and in 2 others, 10 sequential electrocardiograms were studied, whereas in the remainder of the cases 2 to 9 electrocardiograms were analyzed. Except for the case illustrated in Fig. 4 there were very few cases which demonstrated electrocardiographic evidence of increasing severity of stenosis with age using the analysis of the T waves outlined above.

The electrocardiograms of the 49 cases in which the frontal axis of QRS was +45 degrees or more were reviewed by analyzing only the following three criteria indicating severe aortic stenosis and accepting any one as positive evidence: (1) frontal T wave axis superior to +15 degrees, (2) total QRS-T angle (frontal plus horizontal) greater than 100 degrees, (3) R/T ratio in Precordial Lead V_6 greater than 10.

A correct prediction of whether the gradient was greater or less than 50 mm. Hg was made in 86 per cent of the cases and in 2 cases a gradient above 50 mm. Hg was predicted when it was actually 40 and 45 mm. Hg.

Discussion

Widely divergent views have been expressed in regard to the usefulness of the scalar electrocardiogram in assessing the severity of congenital aortic stenosis, particularly in children. Vlad and associates[9] believe that clinical and electrocardiographic criteria for selecting cases for operation are so inaccurate that all children with typical findings of congenital aortic stenosis should undergo left heart catheterization. Other authors suggest that the electrocardiogram is useful in selecting severe cases,[14,15] but there are reports of sudden death in children with congenital aortic stenosis who have normal electrocardiograms.[15,16] Hugenholtz and associates,[17] in 1962, reported that 26 per cent of their 69 patients with significant aortic stenosis had no evidence of left ventricular hypertrophy in their scalar electrocardiograms, whereas 24 per cent of their 26 patients with mild aortic stenosis had definite evidence of left ventricular hypertrophy by voltage or ST-T change criteria. Braunwald and associates[15,4] have discussed the matter well and believe that although some criteria of left ventricular hypertrophy are helpful (i.e., T wave axis, frontal QRS-T angle, R_{V6}, S_{V1}, and R/S V_1 ratio), there are hazards in relying

too heavily on scalar electrocardiograms to decide which cases require operation.

The problem of predicting the severity of congenital aortic stenosis from the scalar electrocardiogram is probably related to the difficulty of establishing useful criteria for left ventricular hypertrophy. These criteria in adults have been discussed by several authors.[illegible]

Most agree that repolarization criteria (or ST-T wave changes) are important in detecting left ventricular hypertrophy on the electrocardiogram. Extensive studies have not been made of the criteria for left ventricular hypertrophy in infants and children, but Keith and associates[11] and Nadas[illegible] have described useful criteria. Walker and Rose[illegible] showed a wide normal variation in voltage parameters normally used for recognizing left ventricular hypertrophy.

In congenital aortic stenosis it is important, from the practical point of view, to detect those cases in which the gradients are of such severity that sudden death may ensue. This happens in approximately 1 or 2 per cent of the cases of congenital aortic stenosis,[14] and aortic valvulotomy is performed to prevent its occurrence. A peak systolic gradient at rest of 50 mm Hg across the stenosis has been widely used as an indicator that surgery should be performed. Although more refined measures of severity, such as determination of aortic valve area and gradient across the valve after exercise or infusion of Isuprel, may be more reliable in selecting cases for operation, sufficient experience has not yet accumulated to adequately assess these techniques.

The children in this series were divided into two groups: those with gradients above and below 50 mm Hg at rest. A study of the commonly used voltage criteria for left ventricular hypertrophy (S in Lead V_1 and V, and R in Leads V_5 and V_6) in these cases failed to yield useful criteria for separating cases of mild stenosis from those of severe stenosis.

In Figs. 6 and 8 the electrocardiogram in a case of congenital aortic stenosis is shown. An R of 38 in Lead V and an S of 35 in Lead V_1 are present, yet the gradient across the valve is only 11 mm Hg. No repolarization abnormalities (ST-T wave changes) are present, i.e., frontal T axis +30 degrees, total QRS-T angle 30 degrees, and R/T in Lead V_6 is 3.8.

In contrast to the unreliability of QRS voltage criteria in the present study and in other studies of scalar electrocardiograms in aortic stenosis, Hugenholtz and Gamboa[illegible] have recently reported findings from Frank lead vectorcardiograms in cases of congenital aortic stenosis. They show an excellent correlation between the maximal spatial vector voltage and the peak left ventricular systolic pressure. Their method appears to be at present the most reliable for predicting the severity of aortic stenosis, but it requires a vectorcardiogram recorder and tedious calculations.

Cassels[illegible] has recently reported a good correlation of measurements of vector loop area (a function of voltage magnitude) with the severity of stenosis.

The various measurements of disturbed left ventricular repolarization in the present series were much more reliable in predicting severe gradients.

Ventricular repolarization occurs during mechanical systole, and one might expect that the imposition of an abnormal systolic load on the left ventricle might disturb ventricular repolarization. Normally the pathway of ventricular repolarization is in a direction opposite to the pathway of ventricular depolarization.[illegible] Since the electrical charges across the cell membranes are reversed during repolarization, the direction of the T wave in the electrocardiogram inscribed during repolarization is usually concordant with the direction of the QRS recorded during depolarization in the same lead. This relationship between the directions of ventricular depolarization and repolarization may be expressed in a different way by saying that the mean manifest electrical axis of the QRS complex in any plane should be roughly parallel to the mean manifest electrical axis of the T wave in the same plane. As ventricular repolarization becomes disturbed in one ventricle, the T-wave axis tends to point away from the affected ventricle, thus widening the QRS-T angle.

In this study it was found that in cases in which the gradients were severe, the T wave direction rotated superiorly and anteriorly until, in children with the

severe stenosis the T wave direction was at 180 degrees to the QRS direction. Fig. 4 shows the electrocardiograms of a patient with congenital aortic stenosis in whom the frontal axis of the T wave was plotted at 5, 8, and 12 years. The T wave axis became progressively elevated and retrograde catheterization when the child was 12 years old showed a gradient of 110 mm. Hg. An aortic valvulotomy was subsequently performed successfully. In our cases, if the frontal axis of the T wave was superior to +15 degrees, the gradient across the aortic valve was usually greater than 50 mm. Hg.

A frontal or horizontal QRS-T angle greater than 60 degrees indicated severe stenosis (Figs. 5 and 7). If the frontal and horizontal QRS-T angles were added together, 100 degrees appeared to separate severe from mild cases. The spatial QRS-T angle (calculated from Helm's tables[7]) was not more reliable than the sum of the frontal and horizontal QRS-T angles, and 60 degrees appeared to divide mild from severe stenosis. Since the calculation of the spatial QRS-T angle is tedious, it would not seem to be worth while.

The R/T ratio in the left precordial leads as described by Sokolow and Lyon[6] is an indirect measurement of the QRS-T angle. With more severe aortic valve gradients, the T wave axis rotates anteriorly, whereas the QRS axis remains stationary or rotates posteriorly. The effect on the scalar electrocardiogram of this divergence of QRS and T axis is to reduce the voltage of T relative to the voltage of R in Leads V_5 and V_6. *The R/T ratio in Leads V_5 and V_6* is a useful measure of severity, and if it exceeds 10, the gradient is probably severe.

It is difficult to explain the observation in this series that in cases in which the frontal QRS axis is less than 45 degrees the *ST-T criteria suggested here are not valid.* Pipberger[11] recently summarized the inaccuracies of the "null contour" vector construction used in *the present study,* and it is possible that some of these factors are more exaggerated in hearts with a horizontal mean frontal QRS axis. Also, conduction defects on the left side may contribute to the left axis deviation and interfere with the use of repolarization criteria. The precision of the methods described in this paper will probably be increased when vectors displayed from simultaneously recorded orthogonal X, Y, and Z axes are analyzed.

This investigation shows that, when one assesses the severity of congenital aortic stenosis from the scalar electrocardiogram, a detailed study of changes in left ventricular repolarization or left ventricular T wave changes by the "mean vector" method is the most reliable technique.

Summary

The scalar electrocardiograms in 65 cases of isolated congenital aortic stenosis in children from 11 months to 15 years of age were studied to determine criteria for assessing the severity of the stenosis. The depth of the S wave in Leads V_1 and V_2 and the height of the R wave in Leads V_5 and V_6 were not helpful and were sometimes misleading. Measurements of disturbed ventricular repolarization (ST-T wave changes) were very useful in predicting severity in cases in which the frontal axis of QRS was +45 degrees or greater.

The following features indicated severe stenosis: (1) a frontal axis of the T wave superior to +15 degrees; (2) the sum of the frontal and horizontal QRS-T angles greater than 100 degrees (the mean direction of QRS or T taken to be at right angles to the lead with a zero or equiphasic deflection in an appropriate reference frame); (3) an R/T ratio in Leads V_5 or V_6 greater than 10.

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Detection of left atrial thrombus by cineangiocardiography

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Systemic embolization occurs at one time or another in about one half of the patients with mitral valve disease who have thrombus material in the left atrium.[1] Furthermore, systemic embolization is a cause of death in 16 to 33 per cent of the patients with untreated mitral valve disease who are over 40 years of age.[2,3] Nonfatal embolism is often associated with serious loss of functional capacity, since 50 per cent of systemic emboli lodge in the cerebral arteries.[3]

The mobilization of left atrial thrombus and the production of systemic emboli at the time of or shortly after closed mitral commissurotomy continues to constitute an important cause of mortality and morbidity from the procedure.[4,5] The current availability of cardiopulmonary bypass gives the surgeon a choice of performing mitral commissurotomy by the closed technique or with the atrium open. If left atrial thrombus is known to be present, the open technique is the procedure of choice and the thrombus can be carefully evacuated under direct vision. Thus, surgical techniques are available for dealing with atrial thrombosis if its presence is known prior to operation.

Left atrial thrombus is more likely to be present in patients who give a history of recent systemic embolism than in patients without embolic episodes, but the history is far from reliable in predicting the current presence or absence of atrial thrombus in a given patient. In a review of 200 cases of systemic embolism occurring at the time of operation, McAllister found only 14 per cent in which there was a previous history of embolism.[6]

Atrial fibrillation complicating mitral stenosis increases the risk of developing left atrial thrombus and embolization.[1,2] Seventy-five to 85 per cent of the patients with systemic emboli will be found to have atrial fibrillation, but not all patients with atrial fibrillation will have atrial thrombosis.[3] A significant number of patients have left atrial thrombus which is unsuspected because they have normal sinus rhythm and have never had recognized systemic emboli.

Cardiac catheterization and contrast radiography are commonly employed in

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the preoperative evaluation of patients with mitral valve disease, but if there is a clear history of embolization and the indications for surgical therapy are present, these procedures are contraindicated. We are not concerned with the group of patients who have a history of embolization but rather with the large group of patients who have no history of embolism who are undergoing preoperative evaluation of hemodynamic and valvular function. In some of these patients, previously unsuspected thrombi can be detected by appropriate examination of the radiographic study, and the surgical approach can be modified accordingly. In other patients with a history of embolism, catheterization may be indicated to clarify the diagnosis, and the presence of thrombus may be confirmed. Left atrial thrombosis has been detected previously by angiocardiography by Soloff and Zatuchni,[8] but we believe that cineangiocardiography is superior to angiocardiography for the detection of thrombus material in the left atrium and will report our experience with this technique.

Clinical material and methods

This study concerns a group of 124 patients with mitral valve disease who underwent transseptal left heart catheterization and cineangiography prior to operation on the mitral valve (Table I). This group represents all of the patients undergoing preoperative cineangiography from November 1960 to November 1964. A catheter was advanced to the right atrium from the right femoral vein by the Seldinger technique[11] and the Brockenbrough transseptal needle[12] was used to puncture the interatrial septum. After pressure measurements were recorded, the catheter was positioned in the left atrium, and an end-hole occluder* was inserted in order to minimize recoil of the catheter during injection by limiting flow to the side holes. The patient was then turned into the right anterior oblique position, and a left atrial cineangiocardiogram was made at 60 frames per second on 35-mm. film during injection of an average of 0.3 to 0.8 ml. per kilogram of body weight of 69 or 75 per cent sodium diatrizoate* by a Gidlund injector at 7 kilograms per square centimeter.

Cineangiograms were carefully studied on an analytical projector.† Valve deformity, calcification, and function were assessed.[13] Evidences of left atrial thrombi were carefully sought and it was possible to recognize three types of left atrial thrombus by cineangiography, as illustrated in Fig. 1: small left auricular appendage clots which may be pedunculated and quite mobile, partial or complete obliteration of the auricular appendage by thrombus with or without extension into the left atrial body, and left atrial body thrombus. For the purposes of this study, the following roentgenographic criteria were found to be consistent with the presence of left atrial thrombus: (1) persistent "fixed" filling defects in the contrast shadow of the body of the left atrium or auricular appendage (Fig. 2); (2) "mobile" filling defects of constant size and shape in the left atrium or appendage (Fig. 3); (3) partial or complete obliteration of the left auricular appendage (Fig. 4); (4) residual staining of a portion of the left atrial wall at a site remote from the point of injection.

Results

The results are summarized in Table I. Ten patients out of the total of 124 in the group were found by cineangiocardiography to have thrombus in the left atrial body or appendage, and in all 10 the presence of a clot was confirmed at operation. One additional patient was thought to have a "mobile" left atrial thrombus by cineangiography, but none was found at the time of open-heart surgery 4 days later and no detectable embolic phenomena had supervened. Four additional patients with left atriograms which were interpreted as being negative for thrombus were subsequently found to have left atrial thrombus at operation. Thus, 14 of 124 (11 per cent) were proved to have left atrial thrombus, and in 71 per cent of these the thrombus was detected preoperatively by cineangiocardiography. Eleven patients

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*Renovist, Squibb; Hypaque, Winthrop-Stearns.
†Tage Arno RG-35

Table I. Comparison of history of systemic embolism and rhythm with cineangiographic and operative findings

History of embolism	Number of patients	Rhythm		Thrombus present	
		NSR	Atrial fibrillation	Cine	Operation
Positive	11	4	7	2	4
Negative	113	58	55	8	10
Total	124	62	62	10	14

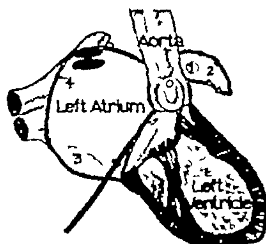


Fig. 1. Left heart chambers and aorta, right anterior oblique (R.A.O.) projection. The stippled areas demonstrate the common types of left atrial thrombi: *1*, pedunculated thrombus in the auricular appendage; *2*, partial obliteration of auricular appendage; *3*, thrombus in the body of the left atrium producing a filling defect; and *4*, a flat mural thrombus which cannot be detected by cineangiography.

had a history of systemic emboli but study was indicated for diagnostic purposes, and only 4 (36 per cent) were found to have left atrial thrombus at operation (Table I). The remaining 113 patients gave no history of embolism and 10 (9 per cent) had left atrial thrombus. Thrombus demonstrated at operation was not detected by cineangiography in 2 patients in each group.

The status of the cardiac rhythm in the entire group of 124 patients is shown in Table I, which indicated that one half of the group had atrial fibrillation at the time of study. The rhythm in the 14 patients found to have left atrial thrombus at operation is shown in Table II. Nine of this group of 14 patients had atrial fibrillation at the time of preoperative evaluation and the other 5 had normal sinus rhythm.

Iatrogenic embolism associated with catheterization occurred in 1 patient in the series, a 35-year-old woman with sinus rhythm and mitral stenosis who developed a right hemiparesis 30 minutes after the completion of a seemingly uneventful catheterization. The presence of residual thrombus was confirmed at operation $3\frac{1}{2}$ weeks later. It is of interest and possible significance that this patient, the only one to develop embolism during a study, gave absolutely no history of embolism.

Discussion

Left heart catheterization and cineangiography were performed in these 124 patients for evaluation of the type and severity of mitral valve disease and the detection of left atrial thrombus was considered to be an important incidental finding. It should be emphasized that a history of embolism was considered to be a relative contraindication to the procedure and in no case was left heart catheterization performed for the sole purpose of demonstrating or ruling out the presence of left atrial thrombus. Cardiac catheterization and left heart cineangiography constitute essential steps in the evaluation of patients with mitral valve disease and thus important additional information may be present if it is systematically sought. Patients with a history of embolism were



Fig. 2 Left atriogram, R.A.O. Thrombus in body of left atrium. The arrow points out a constant filling defect in the left atrial body in the region of the pulmonary veins. The filling defect was constant throughout all phases of the cardiac cycle. Extensive left atrial thrombus was removed at operation.



Fig. 3 Left atriogram, R.A.O.: Pedunculated thrombus in left auricular appendage. Round filling defect (arrow) is seen in the left auricular appendage. In motion the defect was quite mobile and at operation the presence of a pedunculated thrombus was confirmed.

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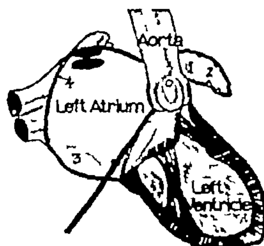


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went mitral commissurotomy without cardiac catheterization, and hence, do not appear in this series.

There are three major reasons for the lack of detection of thrombus when it is present. (1) The image amplifier field does not permit visualization of the entirety of an enlarged left atrium at any one time during filming of the cineangiogram. This problem can be overcome by careful attention to panning the screen over all of the atrium during the filming. (2) Various technical factors make some films inadequate for ruling out the presence of left atrial thrombus. These factors include faulty injection technique (inadequate contrast dose or delivery in the orifice of the valve) and improper x-ray technique (underpenetration or overpenetration of the opacified atrium). (3) Some thrombi are flat and closely adherent to the mural surface and do not distort the contour of the atrium. Since they produce no filling defect in the left atrial contrast shadow they are not recognized.

There are other considerations which may account for the lack of correspondence between the history of embolism and the finding of thrombosis at operation. It is possible that an entire thrombus may be discharged at once, and hence a history of embolism and the absence of thrombus at operation. On the other hand, patients may have a firm, tightly adherent clot which was not discharged prior to operative manipulation. Finally, it is conceivable that left atrial thrombus might form after cardiac catheterization and prior to operation. It is possible, but we think uncommon, that a thrombus may form at the site of trauma sustained during cardiac catheterization,[5] and under these circumstances the surgeon might find thrombus in the atrium of a patient who had both a negative history and a negative radiographic study.

A word of caution should be introduced about the factors which lead to the false-positive diagnosis of left atrial thrombus. The inflow of nonopacified blood from the pulmonary veins into the left atrium which has been opacified by the injection of contrast material produces a filling defect in normal left atria (Fig. 5). Since thrombosis has a predilection for occurring in the posterior portion of the left atrium in the region of the pulmonary veins, the area is

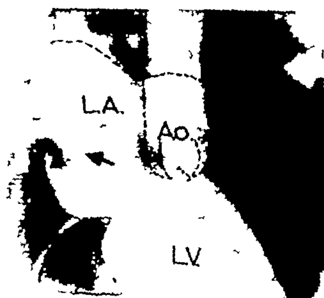


Fig. 5. Left atriogram, R.A.O.: Pulmonary venous inflow. The apparent filling defect designated by the arrow was seen in a patient without left atrial thrombus. Motion-picture projection revealed a change in size and conformation of the radiolucent area with disappearance during atrial contraction as contrast material refluxed into the pulmonary veins.



Fig. 6. Left heart phase (levogram) of pulmonary arteriogram, frontal. Thrombus in body of left atrium. This levogram was obtained after injecting contrast material into the pulmonary artery for the purpose of detecting pulmonary emboli. As contrast material returned to the left atrium, the large filling defect (*arrow*) was seen.

always under suspicion. However, in contrast to the constant filling defect of the left atrial thrombus or myxoma, the defect produced by pulmonary venous inflow changes in size and configuration as the nonopaque blood swirls and mixes with contrast-dyed blood. Pulmonary venous inflow is also distinguished by phasic variations, with maximal dilution in early diastole as the mitral valve opens, attenuation in mid-diastole, and reversal of flow during atrial systole.[22]

In patients in whom mitral stenosis is suspected but in whom the auscultatory findings are unusual and the diagnosis of left atrial thrombus or myxoma is considered, pulmonary arteriography preceding or in lieu of left heart catheterization is a helpful procedure which has been used in our laboratory. Analysis of the return of contrast material to the left atrium on videotape playback or after rapid development of film permits evaluation of that chamber without introducing a catheter into it (Fig. 6). Although the details of the mitral valve are less well seen following pulmonary arteriography, the presence of a mass can often be detected and if present should contraindicate left heart catheterization. The characteristic attachment of the left atrial myxoma to the limbus of the fossa ovalis renders transseptal left atrial catheterization potentially hazardous. If the left atrium is well seen and found to be of normal configuration, the operator may elect to proceed with a transseptal study as part of the same procedure.

Although serial film angiography provides coverage of a larger field and somewhat better resolution, cineangiography has two important advantages in this situation. Appreciation of the flow patterns of pulmonary venous blood entering the opacified left atrium is especially important in the recognition of tumors or thrombi. These flow patterns can be better distinguished from constant filling defects if they are viewed in motion as in the cineradiogram. It is also important to recognize the value of physiologic studies which can be combined more easily with cineradiography than with serial film angiography.

The occurrence of embolism during left heart catheterization in 1 of 124 patients studied represents an incidence of 0.8

per cent and compares favorably with the incidence of embolism in the natural history of mitral stenosis. The avoidance of catheterization in patients with a history of recent embolism and in all patients with a history of embolism and clear signs of pure mitral stenosis minimizes but cannot eliminate the hazard of this catastrophe.

Summary and conclusions

1. A group of 124 patients with mitral valve disease were studied by left heart catheterization and cineangiocardiography prior to mitral commissurotomy.

2. Left atrial thrombus was an incidental finding in 10 patients, 8 of whom had no history of emboli.

3. The presence of thrombus was confirmed at operation in all 10, as well as in 4 additional patients with negative cineangiograms.

4. Iatrogenic cerebral embolism occurred in 1 patient with normal sinus rhythm and no history of embolism.

5. Left atrial cineangiography provides a valuable means of detecting left atrial thrombus, and the risk of iatrogenic embolism is low if patients with a history of recent embolism are excluded.

6. Preoperative catheterization was not performed in patients with a history of embolism if the event had occurred within the preceding 6 weeks or if signs of significant pure mitral stenosis were clearly present.

Addendum

Since this manuscript was submitted for publication 24 additional patients have had left atrial cineangiocardiograms, followed by operation. In 6 patients, thrombus was detected by cineangiography and confirmed at operation. In one patient with a negative cineangiogram a flat thrombus was found at operation low in the atrium extending through the mitral valve. There were no false-positive studies. One patient with atrial fibrillation and a history of left hemiparesis 4 years previously sustained a cerebral embolus after completion of the catheterization.

Parker and associates[16] recently published a report on angiocardiography in the diagnosis of left atrial thrombus.

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Silent mitral insufficiency

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Differential diagnosis between mitral stenosis and mitral stenosis combined with insufficiency is one of the difficult problems of clinical cardiology, especially in cases in which the systolic murmur of *insufficiency is absent*.

In the last 3 years we had the opportunity to study 4 patients who had severe mitral insufficiency without a systolic murmur. Since an accurate diagnosis of the nature and severity of the deformity of the mitral valve is of basic importance in the selection of patients for mitral commissurotomy, this presentation will stress this type of patient in whom the presence of mitral insufficiency may escape recognition.

Case reports

Case 1. N.C., a 17-year-old male, was admitted to the Hippocrates University Hospital of Athens in September 1962 for evaluation of his cardiac condition. A heart murmur had been found a few years before and the patient had complained of shortness of breath for the past 3 years. Recently he had experienced repeated attacks of nocturnal paroxysmal dyspnea with hemoptysis. Digitalis and diuretic therapy was followed by marked improvement. On admission, physical examination revealed the apex beat in the fifth left intercostal space at the mid-clavicular line. A diastolic thrill was felt and a systolic heave was palpable at the left of the sternum. The first heart sound was accentuated. An opening snap and a diastolic rumble with presystolic accentuation were present. P2 was loud. *No systolic murmur was heard.* The liver was enlarged 2 fingerbreadths below the right costal margin. Blood pressure was 125/80 mm. Hg. The rest of the clinical examination was within normal limits. A phonocardiogram (Fig. 1) revealed an opening snap 0.08 second after the aortic component of the second sound; the snap was transmitted to the entire precordium. The tracing also showed a diastolic rumble with presystolic accentuation. *No systolic murmur was recorded.* The Q-first sound distance was 0.10 second. The ECG demonstrated regular sinus rhythm and an axis of 90 degrees. Signs of right ventricular and biatrial hypertrophy were present. The R wave measured 27 mm. in Leads V1 and V2, and a slight S-T and T depression was also present. Because of the fact that the patient was under digitalis therapy and was very thin-chested, these findings were not taken into consideration. Chest x-ray films showed prominence of the pulmonary artery and an enlargement of the right ventricle and right atrium. No heart catheterization was performed. With the diagnosis of mitral stenosis the patient underwent a mitral commissurotomy in October 1962. At operation both atria were found to be slightly dilated. A systolic thrill was felt over the left atrium. The mitral valve was found to be fibrotic but not calcified. Although the anterior commissure was flexible and practically normal, fusion and fixation of the posterior commissure had resulted in stenosis. The mitral opening was estimated to be 1.7 cm. A marked regurgitation (3 plus) was present. No attempt to further open or mobilize the valvular leaflets was made. The patient was discharged from the hospital and was advised to return for corrective mitral valve operation.

Case 2. M. L., a 32-year-old housewife, entered the Hippocrates University Hospital of Athens in March 1963 complaining of exertional dyspnea for the previous 3 years. There was a history of rheumatic fever during childhood, and she had had two normal pregnancies at 22 and 25 years of age. Lately shortness of breath had increased signif-

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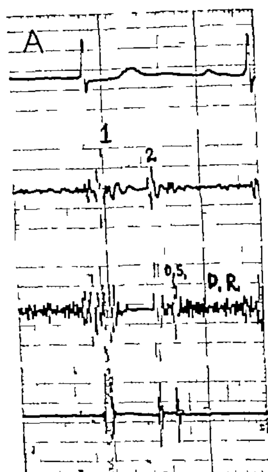


Fig. *1A* Case 1 Phonocardiogram demonstrates first heart sound (*1*), second heart sound (*2*), an opening snap (*O.S.*), and diastolic rumble (*D.R.*). No systolic murmur is present.

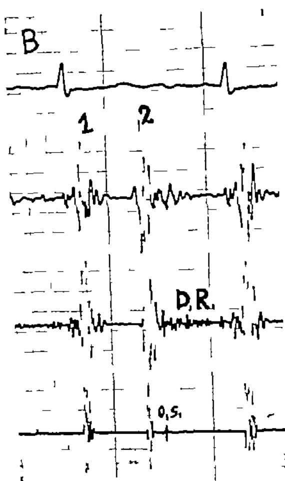


Fig. *1B* Case 2. Phonocardiogram demonstrates first heart sound (*1*), second heart sound (*2*), opening snap (*O.S.*), and diastolic rumble (*D.R.*) No systolic murmur is present.

cantly and there were episodes of paroxysmal nocturnal dyspnea. The patient had been hospitalized in another hospital where she improved after treatment with digitalis and diuretics. Upon admission, physical examination revealed a well-developed woman dyspneic and slightly cyanotic. The apical impulse was in the fifth left intercostal space at the mid-clavicular line. There was systolic hea along the left parasternal line nd P was palpable. On auscultation, the first heart sound was loud and snapping. An opening snap and a diastolic rumble were present. No *systolic murmur was heard*. The jugular eins were distended and the liver was enlarged 3 fingerbreadths below the right costal margin. Blood pressure was 115/75 mm. Hg. The lungs were clear. A phonocardiogram (Fig. 1B) showed first heart sound of great amplitude, an opening snap 0.08 second from the second sound, and a diastolic rumble. The distance Q-first sound was 0.09 second. The ECG showed atrial fibrillation n axis of 90 degrees, incomplete right bundle branch block, and marked clockwise rotation. Slight S-T and T depression was considered to be evidence of digitalis effect. The S wave in Leads V and V was 30 mm. Chest x-ray films revealed an enlarged right ventricle, slightly enlarged left atrium, and prominent pulmonary artery. The peripheral lung markings were decreased. Right heart catheterization proved that pressures in the right entricle and pulmonary artery were slightly increased. The mean pulmonary wedge pressure was 22 mm. Hg, and the tracing was not suggestive of mitral insufficiency. The conclusion arrived t on the basis of the catheterization data was moderate-to-severe mitral stenosis. At operation, the mitral valve was found to be fibrotic with fixed leaflets and partial fusion of both commissures. The opening was estimated t be 2.5 cm. A marked mitral regurgitation (3 plus) was found. An ttempt to fracture the anterior commissure resulted in final opening of 4.0 cm. without increase in the regurgitation. The follow-up proved that, in spit of the additi

opening, the patient did not experience a definite improvement.

Case 3. F. S., a 28-year-old man, was told that his heart condition for the first time at the age of 24 when he complained to his doctor of shortness of breath. Two years later he experienced two attacks of pulmonary edema after physical exertion. Shortness of breath increased progressively, and in January, 1963, he entered the Hippocrates University Hospital for evaluation of his cardiac condition. Physical examination revealed a well-developed man in no acute distress who complained of shortness of breath after exertion. The apex beat was palpable in the fifth left intercostal space. A right ventricular systolic heave and a diastolic thrill were felt. The first heart sound was loud and a diastolic rumble was heard. There was no opening *snap and no systolic murmur. P₂ was accentuated.* The liver was palpable 2 fingerbreadth below the right costal margin. The blood pressure was 125/75 mm. Hg. The rest of the physical examination was within normal limits. A phonocardiogram was recorded and showed (Fig. 1C) a first heart sound of great amplitude, no systolic murmur, a split second sound, and a diastolic rumble. The Q-first sound interval measured 0.07 second. The ECG revealed atrial fibrillation, an axis of +90 degrees, incomplete right bundle branch block, and clockwise rotation. Chest x-ray film revealed an enlarged heart with dilatation of the right ventricle, right atrium, and left atrium, and prominence of the pulmonary artery. A slight left ventricular enlargement was suspected. Pulmonary vascularity was decreased. No calcification of the mitral valve was detected. Right heart catheterization was performed and showed the following pressures (mm. Hg): right ventricle 36/2, pulmonary artery 40/26, pulmonary wedge 18 (mean). A v wave of 20 mm. was present in the latter, with slow y descent and y trough. Because the patient had atrial fibrillation, this wave was not considered to be evidence of regurgitation. Left heart catheterization was also performed. Left ventricular pressure was 85/8 mm. Hg. With the diagnosis of predominant mitral stenosis the patient underwent a mitral valve operation. The surgeon found that the mitral valve was calcified and fixed, and that both commissures were fused. The infundibulum was deformed and the chordae tendineae were shortened and fused. Marked mitral regurgitation was present. Partial fracture of the anterior commissure resulted in a final opening of 3.0 cm.², without an increase in the degree of regurgitation. The patient was considered to be a candidate for total valve replacement.

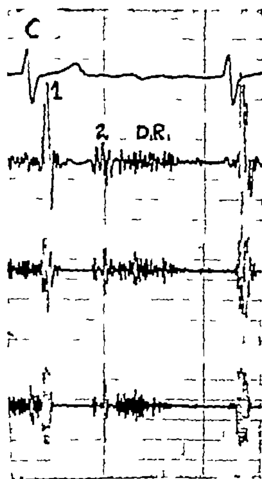


Fig. 1C. Case 3. Phonocardiogram shows first heart sound (*1*) of great amplitude, split second heart sound (*2*), and a diastolic rumble (*D.R.*). No systolic murmur or opening snap are present.

Case 4. T. V., a 40-year-old housewife, was admitted to the Hippocrates University Hospital in December, 1963, complaining of shortness of breath after exertion. She had a history of rheumatic fever at the age of 19. A few years later she started having dyspnea upon exertion; this had increased significantly during the last 3 years. Recently the patient had experienced repeated attacks of paroxysmal *nocturnal dyspnea with bloody sputum. Physical* examination revealed a well-developed, dyspneic, slightly cyanotic woman with distended neck veins. The apical impulse was in the fifth left intercostal space at the mid-clavicular line. A diastolic thrill was present and P₂ was palpable. There was a right ventricular heave at the left of the sternum. On auscultation, the first heart sound was loud. An opening snap was heard over the entire precordium, followed by a diastolic rumble. P₂ was loud and booming. *No systolic murmur was heard.* The edge of the liver was palpated 3 fingerbreadths below the right costal margin. The blood pressure was 115/75 mm. Hg. A phonocardiogram (Fig. 1D) revealed a split first heart sound, no systolic murmur, an opening snap 0.07 second from the second sound, and a diastolic rumble. The Q-first sound interval was 0.09 second. The ECG showed atrial fibrillation, an axis of +90 degrees, and an incomplete right bundle branch block. The R wave was 27 mm. in Lead V₁ and 12 to 15 mm. in Leads V₁ and V₂. Slight S-T and T depression was considered to be evidence of digitalis effect. The chest x-ray film showed an increase in the size of the heart, with enlargement of the right ventricle, right atrium,

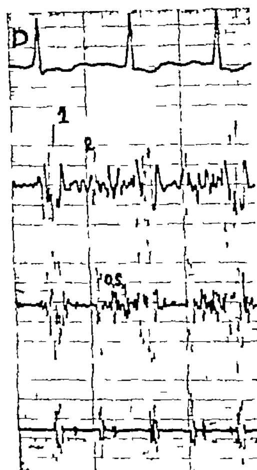


Fig. *1D.* Case 4. Phonocardiogram demonstrates split first heart sound (*1*), second heart sound (*2*), opening snap (*O.S.*), and diastolic rumble (*D.R.*). No systolic murmur is present.

and left atrium and prominent pulmonary artery. Lung vascularity was within normal limits. Right heart catheterization revealed the following pressures (mm. Hg): right ventricle 40/4, pulmonary artery 38/16, pulmonary wedge 15 (mean). The last tracing presented a v wave of 20 mm. with a slow y descent and inconspicuous trough. The conclusion was predominant mitral stenosis. The patient was treated with bed rest, digitalis, and diuretics and improved considerably. In January 1964, she underwent mitral valve operation. The anterior commissure was found to be fibrotic and partially fused. The posterior commissure was fused and calcified. The valve was fixed and the subvalvular system was deformed. The opening was estimated to be 2.8 cm. A marked degree of mitral regurgitation (3 plus) was present. No attempt at dilatation or mobilization was made because of the danger of increasing the regurgitation. The patient remained in the same condition and was considered to be candidate for valve replacement.

Discussion

One of the basic principles in the selection of patients for mitral commissurotomy is the exclusion of cases of severe mitral insufficiency. The recognition of mitral insufficiency is based partly on the existence of an apical systolic murmur. However, as experience increases, it becomes obvious, first, that no relationship exists between the intensity and characteristics of the systolic murmur and the degree of mitral insufficiency and second, that cases of mitral insufficiency without murmur do exist. In spite of the fact that there have been cases in which an unsuspected mitral insufficiency was observed during operation or was detected by other diagnostic means, it is still generally believed that significant mitral regurgitation is unlikely in the absence of a systolic murmur.[1] This is usually a loud pansystolic murmur of medium pitch, starting with the first heart sound and extending to the second sound. Although the first sound is often obscured by the murmur in cases of pure insufficiency, it may remain loud if there is concomitant mitral stenosis.

The present study is based on 4 cases of marked mitral insufficiency combined with mitral stenosis, without a systolic murmur. The diagnosis of mitral insufficiency was missed clinically in all four and most of the laboratory data failed to reveal the presence of mitral insufficiency.

It is known that the intensity of the systolic murmur does not always reflect the degree of valvular damage, because it is influenced by many factors, such as the regurgitant valve area, the flow, the velocity, the pressures across the valve, the anatomic condition of the valvular system, and the viscosity of the blood. With all these factors in mind, one can understand why, with the same degree of mitral regurgitation, the intensity and quality of the systolic murmur can vary. On the other hand, complete absence of the murmur in the presence of marked mitral insufficiency is still a puzzling phenomenon. One can assume that some of the abovementioned factors operate at an extreme degree and may not give rise to a systolic murmur. Another possibility is that the murmur is poorly transmitted to the chest wall as proved by cases in which it can be

recorded only by intracardiac phonocardiography.[3] Occasionally the murmur can diminish or disappear from time to time because of hemodynamic changes. Obviously, one should exclude cases with a systolic murmur caused by tricuspid regurgitation and heard at the apex because of extreme clockwise rotation (false apex).[4] Extracardiac factors, such as pulmonary emphysema, obesity, malformations of the thorax, etc., can also influence the intensity of the murmur, but such factors were not present in our cases. Sometimes a murmur is not audible but is recorded by phonocardiography. In our patients the systolic murmur was neither audible nor recorded by phonocardiography.* Contrary to this, evidence of mitral stenosis (loud first heart sound, opening snap, and diastolic rumble) was present. Although a diminished or absent first heart sound is a sign of severe pure mitral insufficiency, this sound usually remains loud if there is an associated stenosis. The opening snap was absent in one of our patients who had a heavily calcified mitral valve. This supports our previous experience that the absence of an opening snap may signify either calcification of the valve or severe stenosis with a fixed immovable mitral valve. In the other 3 patients the distance of second sound to opening snap was 0.07 to 0.08 second and the distance of Q to first sound was 0.09 to 0.10 second, indicating medium severe degrees of mitral stenosis. It is obvious that, when mitral insufficiency is also present, one should not rely on the value of these intervals. In the above-described cases mitral stenosis was found to be slight to moderate. Luisada[5] states that an opening snap can be present in cases of pure mitral insufficiency but is usually of small amplitude and low pitch. In our cases the opening snap was high pitched and loud. A diastolic rumble was present in all cases. A left ventricular third heart sound was absent in spite of considerable mitral regurgitation. Its presence should be considered to be evidence of left ventricular diastolic overload, even when the systolic murmur is minimal. However, it seems that when mitral stenosis is present, even if it is moderate, a third heart sound is rare.

In the absence of the systolic murmur one has to rely on other clinical or laboratory findings in order to establish the diagnosis of coexisting mitral insufficiency. Tiredness, fatigability, and weakness are considered to be signs of predominant mitral insufficiency[6] but were not predominant in our cases. All of our patients were incapacitated by dyspnea. It is apparent that when mitral insufficiency is associated with mitral stenosis, the degree of elevation of pulmonary pressure is similar to that found in patients with similar degrees of pure stenosis.[7]

Left ventricular enlargement is considered to be a sign of predominant mitral insufficiency. In spite of this, slight-to-moderate degrees of left ventricular enlargement can be missed clinically and the radiologic studies are not always helpful, since it is not easy to estimate the size of the left ventricle in the presence of right ventricular enlargement. In our patients, suspicion of left ventricular enlargement was expressed by some only in one patient who, however, was in severe heart failure. The apex beat was palpable in all patients at the mid-clavicular line and a systolic heave was present parasternally on the left. The lack of evidence of clinical and x-ray changes in the left ventricle can be explained by the fact that mitral insufficiency can be well tolerated. Otherwise one has to accept the fact that moderate left ventricular hypertrophy cannot be detected either clinically or by x-ray examination in a number of cases.

It is generally believed[9,10] that in the presence of marked mitral insufficiency the left atrium is greatly enlarged; however, this fact has been denied.[11,12] In only 2 of our patients was the left atrium slightly enlarged. From our experience, it is not unusual to find that the left atrium is not markedly enlarged in the presence of mitral insufficiency. Probably other factors play an important role in left atrial enlargement. This is also true with mitral stenosis, in which case one can find a varying degree of left atrial enlargement in patients having the same degree of stenosis. An expansile pulsation of the left atrium is considered

*Phonocardiograms were taken by means of a Hellige four-channel machine with adequate dynamic response; the phenomena were recorded in three frequency ranges.

to be a typical diagnostic feature of mitral insufficiency but occasionally it may not be detected. In none of the above mentioned cases was a systolic expansion observed. No calcification of the mitral valve was detected on x-ray examination although in 2 patients calcification was found during the operation.

Although the electrocardiogram is a sensitive index of left ventricular hypertrophy in cases of mitral insufficiency and mitral stenosis the ECG can remain within normal limits or signs of right ventricular hypertrophy may prevail as in our cases. One can assume, in retrospect, that in 3 of the patients there were signs which were not taken into consideration. The slight S-T and T depression in 3 patients was considered to be a digitalis effect. The tall R wave in Lead V_1 (2 patients) and the deep S wave in Leads II and III (1 patient) were not considered to be definite evidence of left ventricular hypertrophy. However it seems that these findings should have justified the diagnosis of left ventricular hypertrophy in the 3 patients. In the fourth patient where were no electrocardiographic signs of left ventricular hypertrophy. It appears that a correlation does not always exist between the work performed by the left ventricle and the electrical evidence of ventricular hypertrophy.

Right heart catheterization was performed in 3 of the patients. The pressures in the right ventricle and pulmonary artery were slightly increased. Mean wedge pressures in the 3 were 15, 18 and 22 mm. Hg respectively. In 2 of them a v wave of 20 and 22 mm. Hg respectively was present, followed by a slow descent and an inconspicuous y trough. Both patients had atrial fibrillation. The conclusion on the basis of the catheterization data was moderate to-severe mitral stenosis. On the other hand, in retrospect the lack of an x descent, the systolic rise in pressure and the tall v waves should have been considered to be evidence of mitral insufficiency.

Left ventricular angiocardiography was not performed, although this is considered to be an effective diagnostic method for the detection and gross estimation of mitral insufficiency. It is possible that left ventricular angiocardiography would have been of value in our cases.

On the basis of all the clinical and laboratory data mentioned all 4 patients were considered to have a moderate-to-severe mitral stenosis that justified subjecting them to commissurotomy. During the operation, the mitral valve opening was found to measure between 1.7 and 2.8 cm.[3] At the same time, a marked mitral regurgitation was observed. The mitral valve was fibrotic fixed and calcified in 2 of the patients. An attempt at further opening improved the stenosis in 2 patients without increasing the severity of regurgitation. In the other 2 patients no intervention was even attempted because the insufficiency was too severe.

From the foregoing it is evident that mitral insufficiency can exist without a systolic murmur. Elkin and associates[12] had the same experience in 5 patients presenting a regurgitant jet during the operation no systolic murmur was detected. Hence one cannot always rely on the absence of the systolic murmur in order to exclude mitral insufficiency. This is even more true in regard to the relationship between the intensity of the systolic murmur and the severity of mitral regurgitation as confirmed by Venner and Holling.[14] Basing the diagnosis on the systolic murmur can create diagnostic errors. Therefore the statement that "the systolic murmur is the most useful criterion in the evaluation of mitral insufficiency"[16] is, in our opinion incorrect. Even phonocardiographic findings are not always sufficient for diagnosis so that the statement that "cardiovascular sound provides the best clue for the evaluation of mitral insufficiency"[16] cannot be confirmed. It should be concluded that the significance of the systolic murmur deserves re-evaluation.[7]

If mitral insufficiency is suspected one should resort to catheterization, angiocardiography and indicator-dilution curves before deciding on surgical intervention.

Summary

Four cases of marked mitral insufficiency without systolic murmur are presented. Absence of the systolic murmur was proved not only by auscultation, but also by phonocardiography. In all cases the diagnosis of mitral insufficiency was missed clinically and mitral stenosis was diagnosed

The patients were incapacitated because of exertional dyspnea and nocturnal paroxysmal dyspnea.

Left ventricular enlargement was not evidenced either clinically or by x-ray examination. The left atrium was slightly enlarged in 2 of the patients but without a systolic expansion. Right ventricular enlargement was found in all patients.

The electrocardiogram proved to be retrospectively the most valuable aid in detecting left ventricular hypertrophy in 3 of the 4 patients.

Right heart catheterization did not help significantly in verifying or excluding the presence of mitral regurgitation.

During the operation a marked degree of mitral regurgitation was found and mitral stenosis was slight to moderate in degree.

It is evident that mitral insufficiency may exist without a systolic murmur. In these cases, auscultation and phonocardiography are unreliable diagnostic means so that other criteria should be taken into consideration.

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Experimental and laboratory reports

Experimental comparison of "parallel grid leads" with simple bipolar, and the SVEC-III, Frank, and McFee-Parungao systems

II. Transverse and vertical leads

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The aim of the present study is a comparison in the homogeneous torso model of Standard Lead I, the transverse leads of the SVEC III,[1] Frank,[2] McFee-Parungao, and parallel grid systems, also of the head-foot, aVF and Frank's vertical leads. A comparison of the corresponding sagittal leads was reported in the preceding paper. The leads under consideration, including grids, were recently compared in the homogeneous torso by Brody and Arzbaecher[4] and theoretically analyzed by Helm and Chou.[6]

Orthogonal leads consisting of sheet-mounted electrodes were first suggested by Reynolds and associates.[7] Since wrapping flexible grids on the chest somewhat impaired uniform projected spacing and thus decreased field uniformity, an attempt was made to more closely approximate the McFee-Johnston[8] ideal of a uniform lead field by introducing platform-mounted parallel grids,[10] and by extending grid area to cover most of the electrically active torso surface. If area is then considered in the relative calibration of the three orthogonal leads, the lead voltage becomes approximately proportional to the codirectional component of the heart's dipole moment.[8,9] One possible consequence of this could be a method of lead calibration which will take the torso dimensions of each patient into account, as discussed hereafter. The effect of torso dimensions on lead sensitivity was shown. Lithium-saturated balsa-wood nonpaste electrodes[4,11] decrease the time and labor cost of using multielectrode grids below that of three standard leads employing paste. They have also been found by Herrmann[12] to be serviceable in conventional electrocardiography.

Method

The previously described experimental setup[4] is used but data are presented in more concise form as follows. The current source is moved to 17 scanning points within the cardiac area of the model (Fig. 1A) and three lead voltages, with the source x, y, and z directed respectively, are recorded as before[4] when voltages from the x, y, and z-directed source were evaluated

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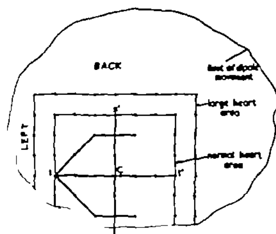


Fig. 1A. Horizontal cut through torso model at level of point C, the approximate center of gravity of the heart. Dipole movement is limited by the walls of the model. The limit of dipole movement corresponds to the projection of the walls of the model on the plane shown, not to torso contour, which is more remote. l-l' and s are transverse and sagittal diameters of the heart in teleradiograms of the subject on whom the torso is molded. Fifty-nine scanning points at 2-cm intervals, at this level and at corresponding points 6 cm. headward and footward of this level.

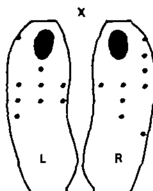


Fig. 1B. The grids employed in the transverse lead of the "parallel" grid lead system.

separately. In the work reported now, the three voltages at each point are summed and the distribution of the summed voltages is evaluated.

Reference plane point voltage current. A point at the crossing of the transverse and sagittal diameters in biplane teleradiograms of the subject on whom the torso was molded (point C, Fig. 1A) is the reference point, and the transverse plane through C is the reference plane. For each lead under study, the codirectional current source (x directed for a transverse lead) is moved to C in the tank and set to yield a lead voltage of 100 mV. This voltage and the corresponding source current are the voltage and current references.

Quantitative definition of local and over all lead distortion. In an ideally accurate (uniform and orthogonal[1]) lead, by keeping the source current at reference value at each of the 177 scanning points, one obtains 177 readings of 100 mV when the source is codirectional to the lead and twice 177 readings of 0 mV when the source is perpendicular to the lead. In an ideally accurate lead, the sum of three readings at each point is 100 + 0 + 0 mV., the mean of all readings in a lead and the standard deviation are 100 and 0 mV., respectively, and the magnitude of the departure from these values is a measure of lead distortion. The advantage of a lead over the control conventional lead is lead standard deviation divided by the standard deviation of the control lead.

The transverse and vertical leads of the parallel grid lead system. The transverse lead consists of two banks of 17 electrodes, one on each side of the chest. Each of the banks is conceived as a 7-row, 3-column grid, where the two upper components of the middle and posterior columns are replaced by the arm. The two top electrodes of the anterior column are in front of the arm (Fig. 1B). The projected spacing of electrodes is 6.5 cm. in this model. The arm and each of the 17 electrodes are connected to a common grid terminal through 100,000-ohm resistors. In the model, metal screws represent electrodes. Possible devices carrying x and y lead grids of balm lithium[12] nonpaste electrodes will be described elsewhere. The vertical lead consists of one electrode each on the head and the left foot.

Results

Transverse leads. The histograms in Fig. 2 show over all lead distortion around the ideal value of 100 mV. The grid appears to be most accurate, Lead I least accurate. Visual distinction between the other leads

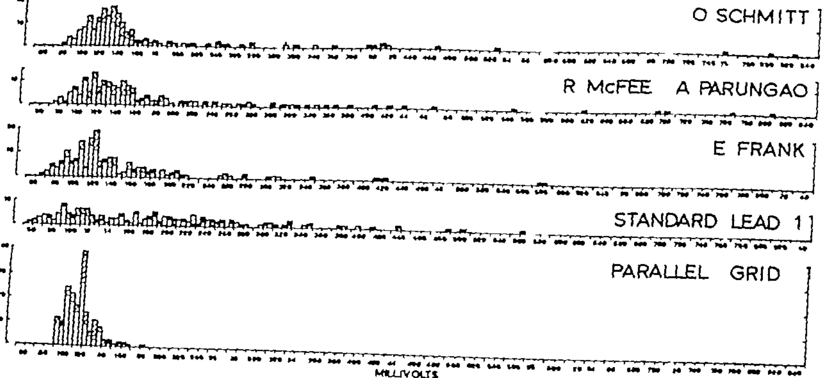


Fig. 2. Trans se leads. With the reference current source consecutively x, y, and directed at 177 scanning points, 177 triple set of 100 + 0 + 0 mV are read in ideally uniform nd orthogonal leads. The histograms show distribution of summed triple sets as obtained experimentally in the leads. The extent of departure from 100 indic tes distortion by the lead. Normal (*unshaded*) and large (*shaded plu un haded*) heart res from 120 and 177 scanning points, respectively.

Table I. The relative accuracy of transverse and sagittal leads defined in terms of variation in lead voltage caused by moving the current source to 120 points ("normal" heart) and 177 points ("large" heart) within the cardiac area of the homogeneous model

Lead	X Y Z Dipole						
	Arithmetic		*Logarithmic*				
	Mean	*S.D.*	*Mean*	*S.D.*	*p = 0.001*	*p = 0.01*	*p = 0.05*
			Vertical Leads				
Normal							
Head-Foot	118.3	11.1	2.071	0.040	a		a
Frank Y	134.1	14.1	2.125	0.034	a	a	a
VF	132.3	22.0	2.116	0.071	b	b	b
Large							
Head-Foot	120.4	12.9	2.078	0.045	a	a	
Frank Y	136.5	16.5	2.132	0.047	a	a	a
VF	137.3	25.8	2.150	0.079	b	b	b
			Transverse Lead				
Normal							
Grid	112.0	12.2	2.047	0.046	a	a	a
Schmitt	138.6	57.0	2.118	0.133	b	b	b
Frank	128.8	45.8	2.087	0.134	b	b	b
McFee	150.0	61.1	2.148	0.149	b	b	b
Lead I	164.0	79.4	2.166	0.207		c	c
Large							
Grid	115.8	16.0	2.060	0.057		a	a
Frank	145.1	77.0	2.123	0.167	b	b	b
Schmitt	162.6	111.5	2.161	0.181	bd	bd	bd
McFee	182.0	121.8	2.202	0.202	bd	bd	bd
Lead I	182.4	94.8	2.207	0.217	d	d	d

Methods which have a letter in common are not significantly different at the stated level of p, whereas two methods which do not have a letter in common do differ significantly. Accuracy, as defined in the text, is inversely related to S.D. and to departure of means from 100.

is not sufficiently clear cut for grading. Table I containing the result of statistical analysis of the data of Fig. 2 again shows least scatter in the grid and greatest scatter and thus greatest over-all distortion in Lead I. In the "normal" heart (120 scanning points, 40 at each of three thoracic levels, Fig. 1) the three corrected leads are indistinguishable from each other statistically, forming a group which is intermediate between the grid and Lead I but closer to the latter than to the grid. In the large heart (59 scanning points at each level, Fig. 1) four grades, in ascending order of distortion, emerge: (1) Grid, (2) Frank, (3) SVEC III and McFee-Parungao, and (4) Standard Lead I. The differences are statistically significant ($p = 0.001$). The advantage of the grid over the other four transverse leads is 3.7 to 7.6-fold in terms of arithmetic S.D., and 2.9 to 4.5-fold in terms of logarithmic S.D. The advantage of the Frank transverse lead over other "corrected" *x* leads

Table II. The mean and scatter around the mean of voltages with the source at the 22 points shown in Fig. 5

Lead	*Mean*	S.D.
Frank y	130.10	8.9
Head Foot	116.3	9.1
aVF	124.6	10.6
Grid x	110.8	12.8
Lead I	154.2	29.9
Frank x	147.4	36.1
McFee x	147.2	37.9
SVEC III x	141.9	45.2

*The reference voltage of 100 mV is not subtracted from each mean as in Fig. 3

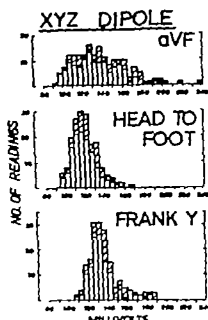


Fig. 3. Vertical leads. With the reference source consecutively x, y, and z directed at 177 scanning points, 177 triple lead-voltage sets of 0 + 100 + 0 mV are obtained in ideally uniform and orthogonal vertical leads. The extent of the departure from 100 mV in the histograms shown indicates departure from ideal accuracy. Normal (*unshaded*) and "large" (*shaded plus unshaded*) heart area from 120 and 177 scanning points, respectively.

and over Standard Lead I is 1.1 to 1.7 fold as arithmetic S.D. and 1.0 to 1.7-fold as logarithmic S.D. The deviation of the means of all measurements in a lead from the ideal mean of 100 is 4-fold to 6-fold greater in "corrected" leads and Lead I than in the grid.

In Table II the means and arithmetic standard deviations within a much smaller heart consisting of 22 points in one plane are shown. The points explored are evident in Fig. 5. In this smaller two-dimensional heart, the Frank and McFee x leads have a 1.3-fold advantage over the SVEC III system. The grid still shows 2.9 times less scatter than the Frank and McFee leads, and 3.5 times less than the SVEC III transverse lead.

Vertical leads. In Fig. 3 aVF shows greater scatter and thus distortion than the head-foot and Frank vertical leads. Visual distinction between the latter two is uncertain. The results in Table I indicate that over-all distortion is slightly less in the head-foot lead than in the Frank y, but the difference is not statistically significant. Lead aVF shows greater distortion than the other two ($p = 0.001$).

Measurement of dipole moment. It was suggested by Barber and Fischmann and shown experimentally for the sagittal grid lead that a fairly good approximation to the measured dipole moment of a current source within the homogeneous torso model is obtained by Equation (1)

$$M = VA/\rho$$

where M is the dipole component codirectional with the lead, V is lead voltage, A is grid area, and ρ is torso resistivity. Equation (1) is the special case of the Gabor-Nelson equation in a uniform field.

In the transverse grid lead, the height of the 7-electrode column multiplied by the greatest sagittal torso diameter at reference level is the measured area of the grid. In the experiment the "effective" grid area obtained with the aid of the equation is 5.7 per cent greater than the measured area. When the mean of three sagittal diameters is used in defining measured area, the discrepancy decreases by 1.3 per cent. The error of approximating the measured dipole moment of an x-directed current source at point C, using the transverse grid and Equation (1), is 2 per cent.

In the vertical head-foot lead, meas-

ured" lead area is the area of the torso cross section at C level treated as an ellipse. The disparity in the model experiment between this value and the "effective" torso area is 4 per cent. Vertical dipole moment was approximated with the head-foot lead to 5 per cent in the model experiment. The validity of Equation (1) in vertical component determination was recently confirmed by Nelson and Matsuoka.[11]

Discussion

A source of lead distortion: unipolar effect of single electrodes or electrode clusters. In Fig. 4 of all leads shown V_6 around its single exploring electrode in the plane of study shows the greatest local bias. Bias is still present but less so in the Frank x lead being dispersed to the two electrodes in this plane. The SVEC III and McFee x leads have two electrodes on the left along a line which is vertical to the explored plane. Local bias is seen near the crossing of the line and the explored plane. Since the electrodes are above and below the bias in this plane is less than in the coplanar V_6 and Frank x. In the grid the current source does not get close to any one electrode without approximating one or more of the others as well. The "unipolar" effect seems to be limited to the immediate neighborhood of the chest wall and is of a lesser degree than in leads with smaller electrode numbers. The Frank and head-foot y leads show little local bias because of the great heart-electrode distance. The proximity of the left arm introduces some local bias in Lead aVF.

Selective cardiac area bias. If, as was done before, Walmsley's[16] transverse cadaver cuts are scaled to the size of the homogeneous model and the heart cut is superimposed on the cardiac area shown in Fig. 1A, 22 of the 59 scanning points in the reference plane lie within or near the myocardium. Fig. 5 shows lead voltages, with the current source at the 22 points. Lead sensitivity to intracardiac current varies regionally because of combined nonuni-

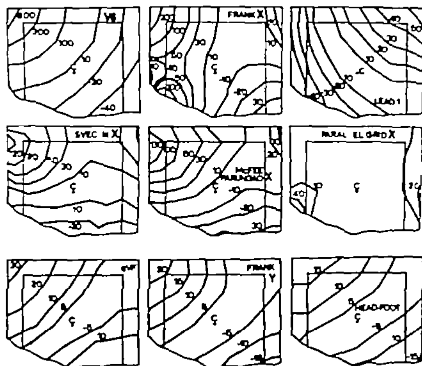


Fig. 4. "Unipolar" bias in the vicinity of electrodes, and its relative absence in the transverse grid and the vertical leads. The reference current source, codirectional with the lead, is moved at C level. The maps show departure from reference lead voltage at C as percentage of that voltage.

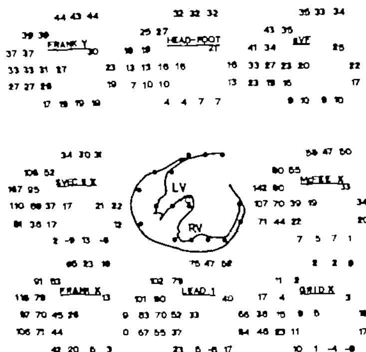


Fig. 5. Regional bias of leads. Twenty-two of the 59 scanning points at C level are within or near the myocardium. The sums of three lead voltages, with the reference source x, y, and z directed, respectively, at these points, are shown after subtraction of the reference voltage of 100 mV. from each figure. Relative magnitudes of the figures shown indicate relative local lead sensitivity.

formity and nonorthogonality of the leads. All transverse leads show an exaggerated response to left, and an attenuated response to right, ventricular and atrial forces. The grid x lead, where the difference is less pronounced than in the other leads, shows mainly left anterior bias. The other x leads show a high degree of bias for the posterior aspect of the left ventricle and the apex. All three vertical leads exhibit left atrial and ventricular bias, but differences are less than in the transverse leads and are least in the head-foot lead.

Lead calibration and grid area. If Z is the calibration factor of a lead, A_e "effective" grid area, V lead voltage, ρ torso resistivity, then

$$(2) \qquad Z = \frac{V}{M} = \frac{V}{V A_e/\rho} = \frac{1}{A_e \rho}$$

In a torso of homogeneous conductivity the scale factors of the three leads Z_x, Z_y, Z_z are related as the reciprocals of the three effective lead areas. "Effective" area defined in the paragraph on dipole moment measurement, equals measured area as also defined within a small error. Thus, if the lead areas of the lead system are measured, the scale factor of the lead system is known. This raises the possibility of individually adapted orthogonal lead calibration, taking body build into account. McFee and Parungao[3] investigated the effect of variation in body shape on lead sensitivity and found that the sensitivity of the sagittal lead increased by as much as 30 per cent in slender flat-chested subjects. In the studies of Hirsch and associates, using an intracardiac dipole in living human subjects, lead magnitude varied with the subject's anatomic proportions and with dipole location. To base lead calibration on area individually, instead of using experimentally derived identical calibration factors for all subjects as is now customary, seems to be one possible way of introducing body build into lead calibration.

Automatic correction for torso shape. Taking the previously[4] described 7 × 5 sagittal grid lead as an example, the electrically active anterior torso surface area

is divided into 35 equal area elements. Each of the 35 electrodes of the grid responds to the sagittal component of the heart's outward diole strength over one area element. With increasing slope sagittal component pickup decreases in proportion to the cosine of the slope. However, this is compensated by the fact that if constant projected electrode spacing is employed, the area corresponding to the electrode unit increases proportionately. This mechanism appears to explain the observation that in model studies using the parallel grid the lead field remained reasonably uniform when a variety of male and female torso shapes was used.[4]

Limitations of the in vivo application of homogeneous model experiments. With one well known exception[17] homogeneous tank experiments played a vital part in the design of corrected systems, and the now widely used Frank system rests entirely on such experiments. Nevertheless, knowledge of the applicability of homogeneous tank data in the living subject is incomplete. This problem as a whole is beyond the scope of the present report but some relevant points are discussed below.

Electrocardiography in a wider sense includes all methods aiming at a definition of the relationship between intracardiac *currents* and torso surface *potentials*. It is reasonable to assume that allowing for a margin of error this relationship in the living subject resembles that in the homogeneous model. There are the following, for the greater part only incompletely explored, clues to the sources and magnitude of the error. In view of the complex resistivity pattern of the human body there are obvious objections to the use of homogeneous torso models.[1] Nonhomogeneous models may have a future place in lead research when technical difficulties are overcome, and when it is shown that interindividual variation of tissue resistivity will not introduce greater error than that inherent in homogeneous models.

Results in homogeneous models using hearts of approximately comparable size are fairly consistent, as shown by the fact that this and the preceding[4] study have yielded results which parallel the following findings reported in Brody and Arzbaecher's[8] careful and technically ingenious comparison of orthogonal leads in a homogeneous model. These authors also found that a satisfactory vertical lead offered no problem; the y head-foot lead was the best and the grid z lead was the second best of the leads examined (axial, Frank, and Schmitt SVEC III leads and a grid z lead). The authors think that the anteroposterior connections of the three corrected systems deviate most widely from ideal conditions, and that this undesirable situation can be improved by the substitution of anteroposterior grid electrodes as the z lead. Brody and Arzbaecher[8] also found that in terms of graphic analysis, none of the lead fields examined closely approximated ideal configuration and that horizontal plane maps of the Frank x and z leads indicated considerable correction toward the center but peripherally x was distorted toward the left and z toward the front by electrode proximity effects, with still greater distortion out of the horizontal plane and SVEC III showed comparable patterns in z. Misalignment and distortions were especially conspicuous in z of SVEC III. These authors thought that lead x of the axial lead showed rather good symmetry of its reciprocal field about the lead axis, but that this design goal was less well approximated in axial lead z, which showed proximity electrode distortion toward the frontal aspect in both the horizontal and sagittal planes.

Anatomic and effective size of the model heart. One essential departure from the original experiments[1,2] is the use of larger hearts and a greater number of scanning points. Both Schmitt and Frank explored hearts smaller than the 425 points on Brody and Arzbaecher's[8] sphere of 17.4-cm. diameter and the "large" heart of 16-cm. diameter employed in the present work.[4] A demand for uniformity over a larger area is more exacting, particularly if enlargement of the area means greater closeness between surface electrodes and the current source. This raises the following questions. Are the size of the cardiac area and the source-to-surface-electrode distance in experiments using hearts of 16 to 17-cm. diameter[4,8] acceptable? How far does the size of the heart influence results? Is the demand for uniformity at a multitude of points rea-

sonable? Although no conclusive answers to these questions are available the following considerations suggest that the hearts are anatomically feasible. The relationship of the heart areas to the radiologically determined transverse (tt') and sagittal (ss') heart diameters of the subject on whom the model was molded is shown in Fig 1A. The width of the transverse diameter of the "normal" heart equals, and that of its posteroanterior diameter is less than tt' and ss' respectively, whereas the 22 point hearts in Fig 5 and the "reduced" 13-point heart in the preceding paper[4] are considerably smaller. Furthermore, if the heart is treated as a hollow sphere having an outer diameter (16 cm.) equal to that of the "large" heart area, and the wall thickness is 15 mm., then the myocardial volume is 550 c.c. If the diameter is that of a smaller heart, say 14.0-cm. diameter and the wall thickness is 12 mm., the volume occupied by the walls is approximately 300 c.c. Since the thickness of the right ventricular wall is typically less than the values quoted, we have feasible heart weights of less than 550 and 300 grams, respectively, and considerably less for the 22 and 13-point hearts.

The validity of the experiments would suffer if minimal electrode-to-heart distance was less than in vivo. The outer irregular line in Fig. 1A indicates the limits of travel of the current source within the model in the plane shown. Since the movement of the source-carrying vertical rod is determined by the waist of the model, the area covered by the source at the level of the heart is a projection of the waist onto the plane explored. The area covered by dipole travel in this plane is thus smaller than the area enclosed by torso circumference. Consequently, the minimal distance between the source and any one x lead electrode varies from 3 to 6 cm., depending on the lead system in question. This degree of heart-electrode proximity is commonly encountered in the living subject and is far exceeded in thin adults and children.

Although it seems to be confirmed that within a large heart in the homogeneous model[4,8] the lead fields of corrected leads show substantially greater nonuniformity than the grid, it does not follow that this is present to the same extent in the living subject. Brody and associates[19] found that the behavior of the heart's forces is approximately vectorial in the living subject, whereas Okada[20] and Geselowitz[21] have indicated that the high conductivity of intracardiac blood could make the forces appear to be more dipolar than they are. A theoretical analysis by Dr. R. McFee and Dr. S. Rush has shown that the low resistance surface layer of muscle girdling the chest can make surface electrodes appear to be several centimeters more distant from the heart than they actually are.[22] This correlates with the finding of Burger and associates[23] that several corrected leads transform with reasonable accuracy into one another and with McFee's[4] observation of a mainly quantitative difference between a grid and the axial system in the living subject, and also with the finding of the reasonably similar information content in orthogonal and conventional leads of the same subjects,[24,25] suggesting that in the living subject, leads may not differ so sharply as they do in the model. On the other hand, it was shown that the dipolarity of the cardiac generator is destroyed if its component dipoles are asymmetrical,[26] or if the excitation front is not closed. The nondipolar content of the heart generator was demonstrated.[27-31]

Thus it seems to be possible that in the living subject the electrically effective size of the heart is less than its anatomic size and that the dimensions and heart-electrode proximity in the model should be less than with anatomically correct heart dimensions. In addition to the three-dimensional "large" and "normal" hearts containing 177 and 120 scanning points, respectively, a 13-point two-dimensional small heart was also employed previously.

A "small" 22-point heart is used in the present study. The standard deviations of the grid x lead change little with the switch to the small heart size (S.D. 16.0, 12.2, 12.8 mV. in order of decreasing size), whereas in the corrected x leads there is a decrease of S.D. and less discrepancy between leads (Tables I and II). As a result of this, the advantage of the grid x lead over corrected leads decreases. The S.D. ratio of grid x to the best corrected x lead is 16.0/77.0 in the larger

17.7/57.0 in the normal, and 12.8/36.1 in the 22 point small heart. Unlike the x leads the performance ratios of the grid z to the best corrected z leads favor the grid as heart size decreases. The grid z to best corrected z S.D. ratios are 8.5/23.5, 6.9/17.4, and 3.4/15.6 in the large, normal, and small hearts, respectively.[4] Although the standard deviations in the Frank and simple bipolar z increase when heart size decreases, grid z remains approximately constant, and all other leads examined show decreasing S.D. In the course of these changes the grid retains a minimal 2.8-fold S.D. advantage (grid x) and a maximal 4.6-fold S.D. advantage (grid z) over the best corresponding corrected lead when heart size decreases. The smallest discrepancy between a grid and a homonymous corrected lead is greater than the maximal discrepancy between any two corrected leads, in any of the heart sizes explored.

The applicability of homogeneous tank data to the axial system is possibly somewhat restricted by the fact that the system is based on tank experiments as well as on data in the living subject. McFee and Parungao[3] tested axial leads by comparison of the axial system with "ideal" grid leads which extended over most of the subject's torso. Over-all determination of dipole moment was said not to be prevented by differences in resistance of heart, muscle, and blood and by anisotropy of the muscle, even though an interpretation of the dipole moment as a vectorial sum of the heart's electromotive forces would be inaccurate.[4]

Summary and conclusions

This, the second of two consecutive papers, reports a comparison of the SVEC III, Frank, and McFee-Parungao transverse leads with Standard Lead I and a "parallel" grid transverse lead, and also a comparison of the Frank, aVF, and head-foot vertical leads. Sagittal leads of these systems were compared in a preceding paper.

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lead voltages with the current source x, y, and z directed, respectively, were obtained at each of the 177 points within the cardiac area of a homogeneous torso model. In an ideally accurate lead the summed voltages at each point are 100 + 0 + 0, and the mean and standard deviation of all measurements are 100 and 0, respectively. The scatter of measurements around these values, shown in histograms and tables, is the measure of lead distortion. The topography of the departure from the ideal distribution is shown in maps.

In terms of logarithmic S.D. the SVEC III, Frank, and McFee-Parungao and grid x leads, in that order, showed a 1.6, 1.6, 1.4, and 4.7 fold advantage respectively over Standard Lead I when 120 of 177 points were sampled (the "normal" heart area, Fig. 14). The corresponding S.D. differences were significant, as were also S.D. differences between the grid and the "corrected" x leads ($p = 0.001$). In 177 point samples ("large" heart) the corresponding advantages were 1.2, 1.3, 1.1, and 3.8, respectively. In this sample the grid and the Frank x were distinguishable statistically from Standard Lead I ($p = 0.001$).

In view of recent work which suggests that the electrically effective size of the heart is less than its anatomic size, lead performance in hearts of varying sizes was studied. The satisfactory uniformity and orthogonality characteristics of the grid persisted in small 13-point and 22-point two-dimensional hearts, as did its apparent advantage over corrected leads.

"Unipolar" effect in the vicinity of electrodes was encountered in all leads studied. This decreased with increasing electrode numbers and with heart-electrode distance and was least in the grid and in y leads. Transverse lead "unipolar" bias resulted in a sligh... ent on anteroseptal forces in the gri... In a pronounced posterobasal and ... accentuation in the corrected lea... leads were more sensitive to left ... right atrial and ventricular force... Lead I, where the opposite appl...

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of variables. Using grid leads seems to make the following variables tractable (1) torso shape, since as surface slope increases, a decrease in pick-up per unit area is balanced by area increase per electrode (2) variable heart size, shape and position, since lead response is relatively uniform throughout the torso (3) intracardiac regional variation due to relatively uniform response throughout the heart (4) interindividual variation of relative lead sensitivity by lead calibration based on the lead area in each patient. Among the variables which remain intractable are effects of the high conductivity of intracardiac blood, dipole cancellation, and torso nonhomogeneity.

On the basis of a comparison of scatter around "ideal" values the relative accuracy of the bipolar corrected, and "parallel grid" leads in the homogeneous model is 1.0, 1.5 and 4.0 approximately in that order. It is self-evident that (a) the more satisfactory performance of the grid in the homogeneous model does not necessarily mean greater accuracy in the living subject (b) even if the grid is more accurate in the living subject it is not known whether increased accuracy would be of a clinically useful order and (c) clinical testing must remain the final arbiter.

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Experimental Schizotrypanum cruzi myocarditis

Correlation between histopathologic and electrocardiographic findings in experimental Chagas' heart disease

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There is a serious controversy in regard to the pathogenesis and the histopathology of Chagas' heart disease. The heart damage produced by *Schizotrypanum cruzi* (*S. cruzi*) has been attributed to a mechanical action of the protozoa,[1,2] to a toxic effect,[1,3,4] to immunologic phenomena,[5] to ischemia secondary to vascular obstruction[6-9] or to rupture of small blood vessels,[10] and to neurogenic mechanisms.[11]

Substantial data have been presented to support each hypothesis, but although certain facts are explained satisfactorily, others have always remained unexplained. This has made the interpretation of some clinical and pathologic findings very difficult. The electrocardiographic abnormalities of ventricular recovery (primary T wave changes and primary ST-T changes) observed in Chagas' myocarditis have been attributed to coronary damage[12] and some pathologists have accepted the existence of coronary damage on the basis of these same electrocardiographic findings.[8] The experimental work presented in this paper is an attempt to study the histopathologic changes in the heart of dogs infected with *S. cruzi* and to correlate these changes with abnormalities in the electrocardiogram.

Material and method

Seventy-two pups, 2 to 6 months old, were infected with a strain of *S. cruzi* that will be defined below. Forty-one of these animals died within 2 months after the inoculation. Sixteen of the survivors were studied within 3 months after inoculation and the other 15 were studied more than 1 year after inoculation, having suffered a variable number of reinfections, as indi-

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cated in Table II. Two adult dogs, 4 and 6 years old, with spontaneous *S. cruzi* infection were also studied. One dog was shown to have been infected for 5 years. The other dog had been born and had always lived in an area in which Chagas' disease was endemic. Xenodiagnosis and complement fixation reactions (CFR) were persistently positive in these two dogs.

The strain of *S. cruzi* used to infect the pups was obtained from the peripheral blood of a patient with acute Chagas' heart disease. He was a young male who had been working in an area in which Chagas' disease was endemic. After 1 month there he started to have fever with involvement of the eyes and lymph nodes, and 15 days later, edema of the face and lower extremities and severe shortness of breath. On physical examination he was found to be in congestive heart failure. His heart was enlarged, as can be seen in Fig. 1. Several pericardial punctures were performed but no fluid was obtained. The electrocardiogram showed sinus tachycardia, low voltage of the T waves, low voltage of the QRS complexes, and primary T wave changes, indicating severe myocardial damage. After 5 months of treatment all the symptoms disappeared and the cardiac shadow and electrocardiogram became normal (Fig. 2).

The strain of *S. cruzi* obtained from this patient was maintained by serial passage in mice. The pups were inoculated intraperitoneally. Serial ECG tracings and blood smears were carried out on the infected dogs in order to determine both the pathogenicity of the parasite and the time of appearance of myocardial damage.

For the recording of standard and precordial leads, the dogs were anesthetized with intraperitoneal 5 per cent chloral hydrate, 0.25 Gm. per kilogram of body weight. The leads used were the three standard limb leads and four precordial leads, two over the right side of the thorax (P_1 and P_2) and two over the left side (P_3 and P_4).

Sixteen dogs were studied with the chest opened as soon as the first electrocardiographic changes appeared, within 3 months after inoculation. This group is considered to be representative of the acute stage of the disease. The other dogs were reinfected repeatedly and were studied with the chest opened more than 1 year after the first inoculation. This second group is representative of the chronic stage of the disease.

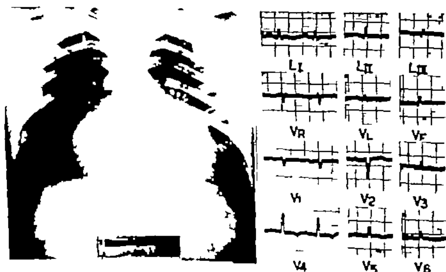


Fig. 1. A 19-year-old male patient with acute Chagas' myocarditis. The heart is globally enlarged and the cardiovascular angles are obliterated. The hilus shadows are prominent. The ECG shows enlargement of the left atrium and disturbance of the conduction medium and abnormal ventricular recovery.

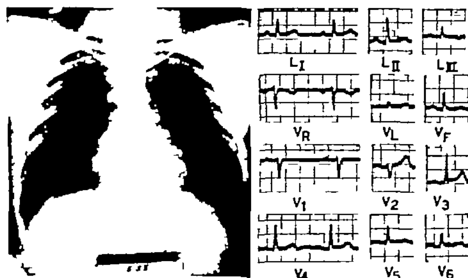


Fig. 2. Records from the same patient as in Fig. 1 after 5 months of treatment. The heart shadow is now normal. In the ECG there is an increase in the voltage of both the P waves and the QRS complexes, and PII is not so wide. The T wave has become positive in the left ventricular leads.

The open-chest studies were carried out as previously described.[12] The dogs were anesthetized with sodium pentobarbital 35 mg. per kilogram of body weight intraperitoneally. A tracheotomy was performed and artificial respiration was started. The thorax was opened using a complete midsternal incision. Arterial and venous pressures were recorded during the entire experiment, and body temperature was kept between 37 and 38°C. Under these conditions unipolar leads were obtained over several points on the epicardium including both atria and both ventricles. When changes in the QRS complex, the ST-T segment, or the T wave were observed, the corresponding areas were marked for more careful and thorough histopathologic study in order to make possible the correlation between electrocardiographic and histologic changes.

The heart of each dog was studied macroscopically and microscopically. Sections were obtained from 21 previously determined areas, as well as from those marked during the open-chest electrocardiographic study. The blocks of tissue were fixed in 10 per cent formaldehyde, pH 7, and imbedded in paraffin. The sections of interventricular septum were fixed in acetone and then imbedded in paraffin. Twenty to 27 sections, 5 microns thick, were cut from each block. Gomori chromic hematoxylin eosin, Gomori trichromic, PAS, and Giemsa stains were used on sections from every block. In some cases the Gridley reticulum stain was also used.

A comparative electrocardiographic and histologic study of 10 dogs without *S. cruzi* kept under the same conditions as the infected dogs, was carried out simultaneously.

Results

Twenty of the 31 dogs which survived after inoculation with *S. cruzi* had electrocardiographic changes within the first 3 months after inoculation. The histologic study of the hearts of these dogs showed abnormalities compatible with the diagnosis of myocarditis in every case. The histologic study in the 11 dogs without electrocardiographic changes revealed mild changes in 7 and none in the other 4. These results can be seen in Tables I and II.

S. cruzi was found in the peripheral blood of 23 dogs, and not in the other 8. It was not found in the blood of any of the control animals. These same 10 controls which were not infected with *S. cruzi* had no abnormalities on histologic examination of the heart. The electrocardiographic tracings obtained daily after the inoculation showed that the first

Table I

Dog No.	*Date of inoculation*	*Date of study*	*S. cruzi in peripheral blood*	*Preinoculation control tracing*	*ECG changes in acute S. cruzi myocarditis*
L_4P	Feb. 20, 1960	March 31, 1960	+	Duration of the P wave, 41.6 msec. P-R interval, 83.3 msec. Voltage of P wave, 3 mm. Voltage of QRS complex, 16 mm.	Increased width of P wave, 83.3 msec. Increased duration of the P-R interval, 148.3 msec. Decreased voltage of P wave, 0.5 mm. Decreased voltage of QRS complex, 8 mm. RBBB. The T wave became negative in the left ventricular leads, P_5 and P_6. Positive shift of ST-T segment in the left precordial leads.
L_3P	Feb. 20, 1960	March 25, 1960	+	P-R interval, 91.6 msec. Voltage of P wave, 2.5 mm.	Increased duration of the P-R interval, 158.3 msec. Decreased voltage of P wave, 0.3 mm. The T wave became negative in L_{II} and L_{III} leads. Positive shift of ST-T segment in L_{II} and in the left precordial leads, P_5 and P_6
L_2P	Feb. 20, 1960	April 7, 1960	+		No changes
L_2P	Feb. 20, 1960	April 28, 1960	+		No changes
L_4P	July 28, 1960	Oct. 3, 1960	+	Voltage of P wave, 4 mm. Voltage of QRS complex, 18 mm.	Decreased voltage of P wave, 0.5 mm. Decreased voltage of QRS complex, 8 mm. The T wave became negative and the ST-T segment presented a positive shift in L_{II} and L_{III} and in the left precordial leads, P_5 and P_6
L_4P	July 28, 1960	Oct. 8, 1960	+		No changes
L_4P	July 28, 1960	Oct. 13, 1960	+		The T wave became flat in all the leads
L_4P	Oct. 11, 1960	Nov. 19, 1960	−		No changes
L_4P	Oct. 11, 1960	Nov. 17, 1960	+		No changes
L_4P	Oct. 11, 1960	Nov. 22, 1960	−		The T wave became negative and the ST-T segment presented a positive shift in the right precordial leads, P_1 and P_2
L_4P	Oct. 11, 1960	Nov. 23, 1960			No changes
L_4P	Oct. 11, 1960	Nov. 24, 1960	+	Duration of the P wave, 48.3 msec. Voltage of P wave, 3.5 mm.	Widening of P wave, 76.6 msec. Decreased voltage of P wave, 0.5 mm. The T wave became negative in L_{II} and L_{III} leads
L_4P	Jan. 30, 1957	April 18, 1957	−		RBBB
L_4P	Jan. 30, 1957	April 30, 1957	−		No changes
L_4P	Jan. 30, 1957	May 4, 1957	+	Duration of the P-R interval, 85 msec.	Increased duration of the P-R interval, 161.6 msec.
L_4P	Jan. 30, 1957	May 7, 1957	+		The T wave became flat in the right precordial leads, P_1 and [illegible]

L, Lot. P, Puppy.

Table II

Dog No.	*Date of inoculation*	*Date of study*	*S. cruzi in peripheral blood*	*Reinoculation (No.)*	*Preinoculation control tracing*	*ECG changes in chronic S. cruzi myocarditis*
L_4I	Jan. 30, 1957	April 21, 1959	+	6	Sinus rhythm. Rate 144	Sinus tachycardia. Rate 230
L_4I	Jan. 30, 1957	April 25, 1959	+	5		The T wave became negative in the right precordial leads, P and P
L_4P	Jan. 30, 1957	April 28, 1959	+	6		No changes
L_4I	Jan. 30, 1957	May 6, 1959	−	6	Sinus rhythm. Rate 160	Sinus tachycardia. Rate 235. Extrasystolic cardiac beats. RBBB. The T wave became negative and the ST-T segment presented a positive shift in L_{II}, L_{III} and in the left precordial leads
L_4I	Jan. 30, 1957	April 20, 1959	−	6		RBBB. The T wave became negative in L_{II} and L_{III}. Positive shift of ST-T in L_I and in the left precordial leads, P and P
L_2P	Feb. 1, 1957	May 9, 1959	+	6		RBBB. The T wave became negative in L_{II} and L_{III} leads. Positive shift of ST-T in the right precordial leads, P and P
L_2P	Feb. 1, 1957	May 16, 1959	−	6	Voltage of QRS complex, 15 mm.	Decreased voltage of QRS complex, 6 mm. The T wave became negative in the left precordial leads, P and P
L_4P	Feb. 5, 1957	June 6, 1959	+	6	Duration of the P wave 43.3 msec. P-R interval, 96.6 msec. Voltage of P wave 4 mm.	Increased width of P wave, 76.6 msec. Atrioventricular conduction disturbance (P-R interval, 151.6 msec.). Decreased voltage of P wave, 0.4 mm. The T wave became negative in [illegible] and L_{III} leads. Positive shift of ST-T segment in the right precordial leads, P and P
L_4P	Feb. 5, 1957	June 6, 1959	+	6	Voltage of the P wave 3.5 mm. P-R interval, 91.6 msec.	Decreased voltage of P wave .07 mm. First-degree A-V block (increased P-R interval, 158.3 msec.). The T wave became negative in the left precordial leads, P and P
L_4P	Feb. 5, 1957	May 3, 1961	+	15		No changes
$L_{11}P$	Jan. 22, 1960	May 13, 1961	+	12	Voltage of the P wave 3.7 mm.	Decreased voltage of P wave, 1 mm. Atrioventricular conduction disturbance (increased P-R interval, 131.6 msec.). The T wave became flat in [illegible] and in the left precordial leads

Table II—Cont'd

Dog No.	*Date of inoculation*	*Date of study*	*S. cruzi in peripheral blood*	*Reinoculations (No.)*	*Preinoculation control tracing*	*ECG changes in chronic S. cruzi myocarditis*
L P	Jan. 22, 1960	Oct. 22, 1961	+	12	Voltage of QRS complex, 17 mm.	Decreased voltage of QRS complex, 7 mm. The T wave became negative in all precordial leads, P_1, P_2, P_3, and P
L P	Jan. 22, 1960	Oct. 24 1961	+	11		No changes
$L_{II}P$	Jan. 22 1960	Nov 3 1961	+	11		No changes
$L_{III}P_1$	Mar 14 1962	Nov 9 1963	+	15	Duration of the P wave, 41.6 msec	Widening of the P wave, 76 6 msec. The T wave became negative in the left precordial leads, P and P_4. Positive shift of the ST T segment in the left precordial leads
SI P	6 years old. Spontaneous S. cruzi infection					Local conduction disturbance (focal block) on the lateral aspect of the right ventricle. QS complex obtained in trabecuzone of the right ventricle. Positive shift of the ST T segment in the epicardial surface of the free wall of the right ventricle
SI P	4 years old. Spontaneous S. cruzi infection					RBBB Negative T wave in right and left precordial leads. Positive shift of the ST T segment n right precordial leads

changes usually took place between 15 and 45 days after the onset of infection The electrocardiographic changes found were sinus tachycardia low voltage and increased width of the P waves, Grade I A V block, right bundle branch block (RBBB) low voltage of the QRS complexes, ventricular premature beats, and T wave and ST T segment changes. These data are also summarized in Tables I and II

Fig 3 illustrates one case in which there were ECG changes during the acute stage of *S cruzi* infection (Dog L_1P_3) The tracing in Fig 3,*A* was obtained before inoculation and can be considered to be a control or reference. Nineteen days after inoculation (Fig 3,*B*) there is an increase in the duration of the QRS complexes, a slurred and indented S in L_{II} and L_{III} in the right precordial leads, P_1 and P_2 there are notched R type QRS complexes. These changes are related to the appearance of a RBBB The ST T segment presents a positive shift and is inferiorly concave in L_{II} and L_{III} and in the left precordial leads P_3 and P there are also inverted T waves in P_3 and P_4. These changes are related to the appearance of lesions and subepicardial ischemia of the lateral wall of the left ventricle The ECG in Fig 3 *C* was taken 33 days after inoculation and shows positive T waves in P_3 and P_4 as a consequence of *improvement in the subepicardial ischemia* of the left ventricle. Finally at 42 days (Fig 3,*D*) there is low voltage of the P waves, a further decrease in the voltage of the QRS complexes, less positive shift of ST T in L_{II} and L_{III} and a low T wave in L_1 P_3 and P_4. These

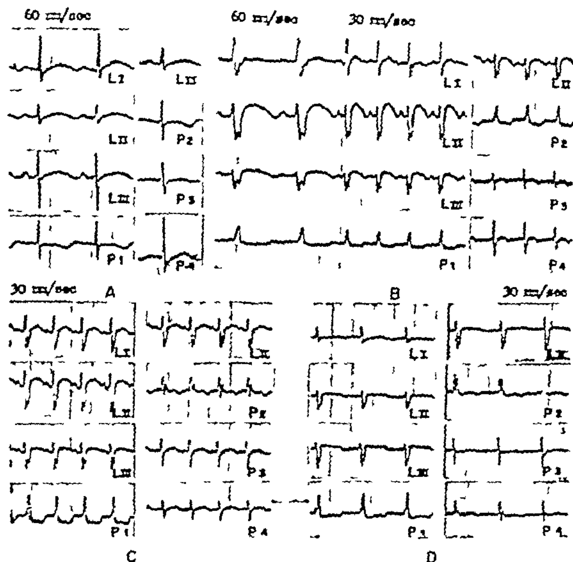


Fig. 3. Evolution of the ECG in pup L. P. from the moment of inoculation with S. cruzi. A, Preinoculation control tracing. B, Small voltage of QRS, RBBB, subepicardial ischemia and lesion of the lateral wall of the left ventricle. C, Persistence of RBBB and improvement in the ischemia. D, Greater decrease in QRS voltage, decrease in lesion and recurrence of ischemia subepicardially in the lateral wall of the left ventricle and persistence of the RBBB.

changes indicate a decrease in the posterior subepicardial lesion and reappearance of subepicardial ischemia in the lateral surface of the left ventricle.

On gross inspection, the hearts of dogs suffering from acute or chronic Chagas infection were globular, flaccid, dilated, and heavier than normal. No abnormalities of the endocardium, A-V valves, or semilunar valves were observed. In some cases, white areas corresponding to subepicardial fibrosis were found on the epicardial surface of the heart. The heart of a dog (SI P_3) with spontaneous infection by S. cruzi of 5 years' duration can be seen in Fig. 4. It was enlarged (weight of 280 grams) and, when placed on the table before being fixed in formalin, it collapsed and folded like a piece of cloth. There was a whitish area 30 mm in diameter on the epicardial surface over the trabecular area of the right ventricle, under which intense fibrosis

Table III

Dog No.	Time elapsed since inoculation	*Histopathologic findings in acute Chagas' heart disease*
L_4P	1 mo. 11 days	*LA* Very dense interstitial infiltration. *RA* Dense infiltration, a few leishmanial clumps. *LV* Dense focal infiltration. *RV* Very dense interstitial infiltration, diffuse interstitial edema, fragmentation of myocardial fibers and scarce leishmanial clumps. *IS* Dense diffuse infiltrates. Scarce leishmanial clumps. Interstitial infiltration in the bundle of His
L_4P	1 mo. 5 days	*LA* Very dense infiltration and some leishmanial clumps. *RA* Same as LA. *LV* Diffuse infiltrates of variable density, scanty leishmanial clumps, fragmentation of myofibers. *RV* Dense, diffuse infiltration, leishmanial clumps. *IS* Dense infiltrates and leishmanial clumps. Infiltration of the left bundle branch
L_4P	1 mo. 15 days	*LA* Diffuse infiltration. *LV* Scanty small infiltrates, leishmanial clumps. *RV* Scarce infiltrates. *IS*. Diffuse infiltration
L_4P	2 mo. 8 days	*LA* Scarce areas of interstitial infiltration. *RA* Diffuse infiltrates. *RV* Small, very scarce infiltrates. *IS* A few areas of infiltration and clumps of Leishmania
L_4P	2 mo. 5 days	*LA* Dense diffuse infiltrates. *RA* Same as LA. *LV* Same as LA and RA, and interstitial edema, fragmentation of myofibers, proliferation of connective tissue and isolated leishmanial clumps. *RV* Same as RV without connective tissue proliferation. *IS* Dense, diffuse infiltration. Very scarce leishmanial clumps
L_4P	2 mo. 10 days	No abnormalities found
L_4P	1 mo. 23 days	*AI* Diffuse infiltrates. *RA* Focal infiltrates and fragmentation of myofibers. *LV* Dense, diffuse infiltration and myofiber fragmentation. *RV* Dense diffuse infiltrates, leishmanial clumps
L_4P_1	1 mo. 8 days	No abnormalities found
L_4P	1 mo. 6 days	*RA* Moderate interstitial infiltration. *LV* Scarce infiltrates, relatively more abundant in the diaphragmatic wall. *RV* Moderate interstitial infiltration, scanty leishmanial clumps. *IS* Slight interstitial infiltration
L_4P	1 mo. 11 days	*LA* Very intense and dense infiltration, myofiber fragmentation. *LV* Dense focal infiltrates, myofiber fragmentation. *RV* Dense, diffuse infiltrates, myofiber fragmentation; moderate connective tissue proliferation. *IS* Focal and diffuse infiltrates
L_4P	1 mo. 12 days	No abnormalities found
L_4P	1 mo. 13 days	*LA* Diffuse focal infiltration. *RA* Focal infiltrates. *LV* Dense focal infiltrates arranged in clusters containing degenerated myocardial fibers. *RV* Diffuse infiltrates. *IS* Focal infiltration, myofibers with degenerative processes
L_4P	2 mo. 18 days	*LA* Dense interstitial infiltrates. *LV* Small, scarce interstitial infiltrates. *RV* Dense infiltrates, fragmentation of myofibers. *IS* Focal and diffuse infiltrates, myofiber fragmentation, interstitial infiltration of the bundle of His
L_4P_1	2 mo. 20 days	*LA* Scarce very dense infiltrates, myofiber fragmentation. *RA* Scarce infiltrates. *LV* Scarce focal infiltrates, small and dense with myofiber fragmentation. *RV* Dense focal infiltration with myofiber destruction. *IS*. Isolated infiltrates in the bundle of His, fragmentation of myofibers
L_4P	3 mo. 4 days	*RA* Infiltrates in moderate numbers, fragmentation of myofibers. *LV* Dense focal infiltration, and myofiber fragmentation. *RV* Dense focal infiltrates, myofiber fragmentation. *IS* Interstitial infiltrates, fragmentation of myofibers. Infiltration of the bundle of His
L_4P	3 mo. [illegible] days	*LA* Diffuse infiltrates. *RA* Same as LA. *LV* Focal infiltration, fragmentation of myofibers. *RV* Diffuse infiltrates

LA Left atrium. *RA* Right atrium. *LV* Left ventricle. *RV* Right ventricle. *IS* Interventricular [illegible]

Table IV

Dog No.	Time elapsed since inoculation	Histopathologic findings in chronic Chagas' heart disease
LaP₁	2 yr 2 mo 12 days	*RA* Scanty subendocardial infiltrates. *LV* Scarce infiltrates in the posterior wall. *RV* Mild, diffuse infiltrates in anterior and posterior walls. *IS* Connective tissue proliferation between the fibers of the bundle of His
LaP	2 yr 2 mo 26 days	*LA* Mild diffuse inflammatory infiltration on the posterior wall. *RA* Mild diffuse infiltration in the anterior wall and focal infiltration in the interatrial septum. *LV* Scanty infiltrates in the anterior wall; connective tissue proliferation in the posterior wall. *RV* Subendocardial infiltrates and mild interstitial connective tissue proliferation in the anterior wall; scarce, isolated infiltrates subepicardially in the posterior and lateral walls. *IS* Small infiltrates between fibers of the bundle of His
LaP	2 yr 3 mo.	No abnormalities found
LaP	2 yr 4 mo 7 days	*RA* Focal, subepicardial infiltrates in the anterior wall. *LV* Focal infiltrates and scar tissue disseminated over the anterior wall. *RV* Perivascular inflammatory infiltrates in the anterior wall; slight connective tissue proliferation in the right wall. *IS* Focal infiltration and small area of scar tissue
LaP	2 yr 3 mo 21 days	*LA* Scarce focal infiltrates. *LV* Scarce small inflammatory infiltrates, myofiber fragmentation and connective tissue proliferation. *RV* Diffuse inflammatory infiltration, myofiber fragmentation and scar formation; focal infiltrates in the right wall. *IS* Focal infiltrates, perivascular and in the right bundle branch
LaP	2 yr 3 mo. 8 days	*LA* A few focal infiltrates in the auricular appendage; dense focal infiltrates in the posterior wall. *RA* Diffuse infiltration and interstitial edema, fragmentation of myocardial fibers and interstitial connective tissue proliferation in the anterior wall and in the interatrial septum. *LV* Scarce focal, subendocardial infiltrates in the posterior wall; myofiber fragmentation and proliferation of connective tissue. *RV* Scarce small infiltrates. *IS* Small interstitial infiltrates and interstitial fibrosis between the fibers of the conduction tissue
LaP	3 yr 3 mo 8 days	*LA* Diffuse inflammatory infiltration. *RA* Intense epicardial infiltration and slight focal infiltration in the interatrial septum. *LV* Interstitial connective tissue proliferation. *RV* Small focal infiltrates and slight connective tissue proliferation in the posterior wall; scarce infiltrates, myofiber fragmentation and small areas of scar tissue in the right wall
LaP	2 yr 4 mo	*LA* Diffuse infiltrates and small areas of scar tissue. *RA* Small areas of scar tissue. *LV* Scarce inflammatory infiltrates, fragmentation of fibers and scar tissue. *RV* Focal infiltrates, myofiber fragmentation and scar formation in small areas
LaP	2 yr 4 mo. 8 days	*LA* Small, diffuse infiltrates and connective tissue proliferation in the auricular appendage; intense infiltration and scar formation in the posterior wall. *RA* Intense infiltration. *LV* Scarce small inflammatory infiltrates, connective tissue proliferation and scar formation, mainly near the epicardium. *RV* Isolated scar formation mainly near the epicardium. *RV* Isolated and diffuse infiltrates, myofiber fragmentation and connective tissue proliferation. *IS* Intense infiltration, myofiber fragmentation, and scar formation beneath the right bundle branch in the myocardial mass
LaP₄	4 yr 2 mo. 28 days	*LV* Scarce inflammatory infiltrates, myofiber fragmentation and small areas of scar tissue. *RV* Scarce focal infiltrates, small areas of scar formation

Table IV—Cont'd

Dog N°	Time elapsed since inoculation	Histopathologic findings in chronic Chagas' heart disease
L P	1 yr 3 mo. 21 days	*LA* Numerous epicardial infiltrates. Degeneration of myofibers connective tissue proliferation. *RA* Infiltrates. *LV* Diffuse epicardial infiltrates. *RV* Diffuse subendocardial infiltrates and scanty connective tissue proliferation. *IS* Slight, diffuse infiltration in the endocardium of the right ventricle degeneration of myofibers
L P	1 yr 9 mo.	*LA* Slight infiltration in epicardium Increased connective tissue *RA* Fibroblastic proliferation and diffuse infiltration in the epicardium. *LV* Severe subendocardial infiltration degenerated myofibers connective tissue proliferation many areas of scar tissue. *RV* Severe inflammatory infiltration with damaged fibers profuse fibroblastic proliferation
L P	1 yr 9 mo 2 days	*LA* Diffuse inflammatory infiltrates and fibroblastic reaction. *RA* Diffuse infiltrates *LV* Diffuse infiltration. *RV* Severe infiltration and damaged myofibers. *IS* Slight, diffuse infiltration and minimal fibroblastic reaction
L P	1 yr 9 mo. 11 days	*LA* Scarce focal infiltration. *LV* Scarce focal and diffuse infiltration minimal, disseminated fibrotic foci. *RV* Intense conglomerated subepicardial infiltrates changes in myofibers connective tissue proliferation *IS* Great infiltrates in the upper portion of the septum degenerated myofibers infiltrates between the fibers of the right bundle branch
L P	1 yr 6 mo.	*LA* Diffuse inflammatory infiltrates and fibroblastic reaction. *RA* Diffuse infiltrates. *LV* Severe inflammatory infiltration with fibroblastic proliferation. *RV* Diffuse infiltrates and degeneration of myofibers
SI-R	Spontaneous S cruzi infection	The heart was enlarged and globular Bright whitish plaques of different sizes appeared over all the epicardial surface of both ventricles. The right ventricular wall was very thin and specked in grayish yellow with zones of fibrosis. There was an organized thrombus inside the tip of the right ventricle. *LA* Diffuse inflammatory infiltrates and fibroblastic reaction *RA* Severe fibroblastic proliferation with severe inflammatory infiltration. *LV* Severe inflammatory infiltration with fibroblastic proliferation. *RV* Intense inflammatory infiltration dissociated muscle fibers with various forms of degeneration and diffuse proliferation of connective tissue
SI-R	Spontaneous S. cruzi infection	There was dilatation of all four cavities, mainly of the right ventricle. *LA* Diffuse inflammatory infiltrates and fibroblastic reaction. *RA* Severe inflammatory infiltrates and profuse fibroblastic proliferation *LV* Diffuse infiltration and fibroblastic reaction. *RV* Severe infiltration and damaged myofibers with intense proliferation of connective tissue

was found Other smaller areas of fibrosis were found on the epicardial surface of both ventricles. Both atria and ventricles were dilated There was an organized thrombus inside the tip of the right ventricle, underlying the large area of fibrosis described above The free walls of both ventricles were thin 9 mm halfway down in the left ventricle and 1 mm at the tip of the right ventricle, on the larger zone of dense fibrosis. The coronary arteries were slightly dilated

Microscopic study of the cases of acute Chagas infection revealed the existence of an inflammatory process constituted by dense interstitial lymphocytic and histiocytic infiltration, both focal and diffuse in irregular distribution (Fig 5,A C) fragmentation of muscular fibers, without scar formation (Fig 5,B) inflammatory infiltration around the bundle of His (Fig 6,A) and clumps of leishmanial forms of *S cruzi* (Fig 6,B C)—these last 7 cases. Inflammatory infiltrates wer

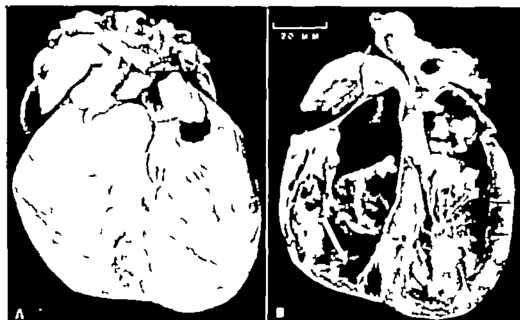


Fig 4 The heart of a dog (SI P) 5 years after the beginning of spontaneous infection with S cruzi. A The heart is enlarged and globular Bright, whitish plaques of different sizes appear over all of the epicardial surface of both ventricles B There is dilatation of all four cavities, mainly of the right ventricle The right ventricular wall is very thin and specked with grayish yellow with zones of fibrosis. The tip of the right ventricle is particularly thin (1 mm) and grayish white This is an area of full-thickness fibrosis. The arrow points to a partly organized thrombus. The valves are normal.

also seen in the walls of some arterioles

No morphologic data compatible with the diagnosis of myocarditis were found in 3 cases (L_4I_4, L_4P_1 and L_4I_3) Sympathetic ganglia were studied in some cases and no abnormalities were found in them

A chronic diffuse inflammatory process was seen in the chronic cases. The interstitial infiltrate, again both focal and diffuse, and of variable intensity contained lymphocytes histiocytes, and plasma cells, scattered in an apparently haphazard fashion in both ventricles, in both atria and in the interventricular septum (Fig 7,*A B*) Fragmentation of myocardial fibers was also seen (Fig 8,*A*,*B*) but small scars were also present (Fig 8,*A C*) In most sections there was a diffuse proliferation of the connective tissue of variable degree. Several types of lesions of the myocardial fibers were observed Eosinophilic leukocytes were scarce. Inflammatory infiltration in the vicinity of the bundle of His and its branches was also seen (Fig 7 *C*) No vascular lesions were found

Clumps of Leishmania were found in only one case In one other case the heart was entirely normal

It must be pointed out that the most severe lesions were to be found in the right ventricle and in the atria.

The unipolar leads obtained with the electrode over various points on the epicardial surface of the heart presented the following abnormalities alterations of the QRS complex such as those found in electrically dead areas widening of the QRS complexes, the consequence in some cases, of a RBBB and in others, of local conduction defects (local block) positive or negative shift of the ST T segment and peaked symmetrical negative T waves. A definite correlation was found between the sites having histologic abnormalities and those from which abnormal ECG recordings were obtained The areas with the most intense inflammatory process were always those with maximum ST T shifts and T wave changes, whereas the ones with discrete infiltration gave rise to slightly abnormal ECG tracings. Some



Fig. 5. Acute myocarditis in dogs inoculated with *S. cruzi*. *A*, Dense diffuse infiltration with round cells and interstitial edema separating muscle fiber (hematoxylin and eosin, ×128). *B*, The muscle fibers are separated by a dense mononuclear infiltration which contains fragments of fibers and foci of myocytolysis (hematoxylin and eosin, ×128). *C*, Dense focal infiltration with round cells, most of which are histiocytes with what seems to be elling of fiber (hematoxylin and eosin, ×320).

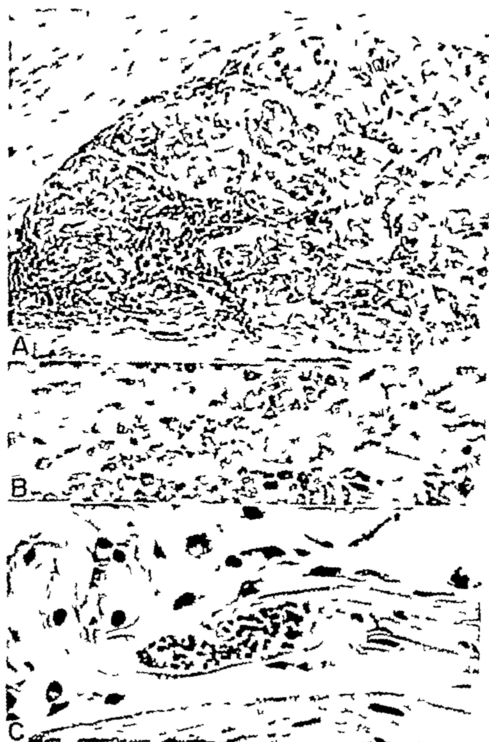


Fig. 6. Acute myocarditis. *A*, Interstitial inflammatory infiltration around the bundle of *His* (hematoxylin and eosin, ×128). *B*, Cross section of myocardial fiber which contains leishmanial forms of *S. cruzi* and is surrounded by inflammatory infiltration (hematoxylin and eosin, ×320). *C*, Leishmanial forms of *S. cruzi* in a myocardial fiber (hematoxylin and eosin, ×312).



Fig. 7. Heart sections with chronic Chagas' heart disease. *A*, Interstitial mononuclear cell infiltration in the interatrial septum (hematoxylin and eosin, ×128). *B*, Dense mononuclear cell infiltration in the interventricular septum; degenerated myocardial fibers (hematoxylin and eosin, ×320). *C*, Infiltration in the left branch of the bundle of His (hematoxylin and eosin, ×128).



Fig. 8. Chronic myocarditis. *A*, Scar tissue and fragmentation of myocardial fibers in the left atrium (Gomori trichromic ×320). *B*, Myocytolysis and fragmentation of myocardial fibers (Gomori trichromic ×512). *C*, Scar on the free wall of the left ventricle (Gomori trichromic ×512).

areas with scanty and diffuse infiltration gave normal epicardial ECG tracings. This correlation is depicted in Fig. 9. The unipolar lead obtained over *A* showed qRsR'S complexes, and histologic examination of the same area showed intense infiltration with lymphocytes, histiocytes, and plasma cells, edema, dissociated muscle fibers (some atrophic and others undergoing various forms of degeneration) and diffuse proliferation of connective tissue. At *B*, Rs complexes and negative shift of the ST-T segment were seen. Histologic study of this area demonstrated the presence of an intense inflammatory process located subendocardially. The unipolar lead taken at *C* has Qrs complexes, slight positive shift of the ST-T segment, and negative T waves. Here the pathology was subepicardial and consisted of moderate infiltration and dissociated, sometimes atrophic, muscle fibers, interspersed with areas of dense scar tissue. Finally, at *D* there were QS complexes, marked positive shift of ST-T segments, and T wave changes. The underlying tissue was fibrotic and markedly reduced in thickness. It also had cellular infiltrates. This was a case of focal myocarditis evolving fibrosis.

Discussion

The strain of *S. cruzi* used in these experiments was definitely pathogenic as proved by its effect on the heart of the patient from who it was isolated and by the myocardial damage it produced in the inoculated pups. Forty-one of the 72 inoculated dogs died with myocardial lesions within 2 months. This mortality, 56.9 per cent, is the same as that reported by Magalhaes[11] in his infected dogs.

The diagnosis of myocarditis was established on the basis of pathologic findings, in 27 of the 31 surviving dogs (87.1 per cent), whereas only 4 animals (12.9 per cent) remained free of heart damage. It must be mentioned that these 4 dogs without histologic abnormalities also had

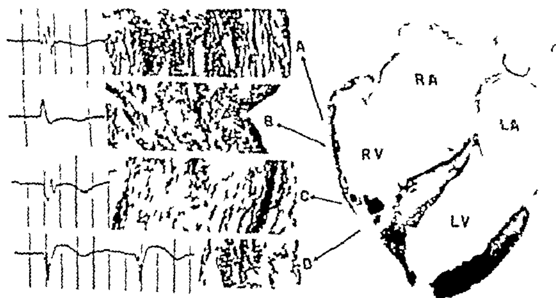


Fig. 9. Correlation between ECG changes and histologic findings in dogs with chronic Chagas myocarditis. *A*. The tracing mimics that of a RBBB and the section of the underlying muscle tissue shows inflammatory infiltration between atrophic and degenerated myocardial fibers, with scanty proliferation of connective tissue. *B*. The unipolar lead indicates the presence of a subendocardial lesion, and the histologic examination reveals intense edema and interstitial inflammatory infiltration subendocardially. *C*. Qrs complexes, subepicardial ischemia and lesion in the ECG and an area of subepicardial focal fibrosis with diffuse cellular infiltration; myocardial fibers are dissociated and some are atrophic. *D*. The unipolar lead shows an area of necrosis (QS complex) with severe subepicardial ischemia and lesion, whereas histologic examination reveals full-thickness fibrosis, marked decrease in thickness of the wall, and inflammatory infiltration.

a normal ECG. Electrocardiographic abnormalities were found in 20 of the 27 dogs with histologically abnormal hearts. In the other 7 dogs, in which the ECG was invariably normal, cellular infiltrates, myocardial fiber degeneration, and interstitial fibrosis were minimal.

These data lead to the conclusion that when there are ECG changes there will always be histologic abnormalities. On the other hand, ECG changes occurred in only 74 per cent of the dogs with myocardial pathology. These values are similar to those reported by other authors[1, 17] in studies on human beings and show the usefulness of the ECG in the diagnosis of myocardial damage.

S. cruzi was frequently found in the blood of the surviving pups (74.2 per cent), appearing in the blood stream between 2 and 4 weeks after inoculation and disappearing from it about 4 weeks later, as was observed by Chagas[14] in his patients and by Torres[3] in his experimentally infected animals.

The presence of circulating forms of *S. cruzi* was not always followed by histologic evidence of heart damage: in 3 cases of this series in which the parasites were found in the blood, the histology of the heart was normal. Conversely, absence of the organism from the blood does not rule out the possibility of myocardial lesions: in 7 of the 8 dogs in this series in which *S. cruzi* was not found in the blood, the histologic picture was compatible with a diagnosis of Chagas' myocarditis.

The absence of circulating forms of *S. cruzi* can be the result of low-density or short-duration parasitemia.[18] Short-term parasitemia seems to be related to the early appearance of specific immunologic factors.[1, 18]

Three main histologic abnormalities were found during the acute phase of Chagas' myocarditis in the material studied: (1) edema and infiltration with lymphocytes, histiocytes, and plasma cells, both focal and diffuse, irregular in intensity and extension and apparently distributed haphazardly; (2) fragmentation of muscle fibers without scar formation; (3) myocardial fibers containing leishmanial forms of *S. cruzi*.

In the chronic cases the inflammatory process had the following characteristics: (1) edema and infiltration similar to that observed in the acute cases; (2) myocardial fibers with several characteristics: (a) weak cytoplasmic staining, (b) modified nuclear staining, (c) loss of striae, (d) granular, vacuolar, or fatty degeneration, (e) myocytolysis, and (f) fragmentation; (3) proliferation of connective tissue with scar formation, irregular in extension and intensity.

These are the histologic findings characteristic of the acute and chronic stages of *S. cruzi* myocarditis as they were first described by Chagas[1] and later confirmed by almost all of the investigators in this field.[3, 5, 10, 15, 21] In this series of experiments the histologic picture always correlated positively with the duration of the infection.

In order to interpret the histologic findings in relation to their cause it is necessary to keep in mind the fact that degenerated myocardial fibers were found only where edema and cellular infiltrate were important. This finding is in agreement with that of other investigators.[3, 5, 10, 15] The proliferation of connective tissue was also found exclusively where inflammation and degenerated myocardial fibers were present. Under these circumstances it seems to be improbable that the myocardial fiber degeneration is due to the liberation of a toxin from other fibers ruptured by leishmanial forms of *S. cruzi*.[1, 3, 4] If that were the case, degenerated myocardial fibers should be found only in the vicinity of clumps of parasites, which is in direct disagreement with the results of these experiments and those of other authors.[10, 21] Furthermore, Lemos Torres[22] points out the disproportion between the extremely small number of fibers containing leishmanial forms of *S. cruzi* and the great extension of diffuse myocardial lesions.

The ECG changes seen in the unipolar epicardial leads were related to and proportionate to the histologic abnormalities. ST-T segment and T waves changes were seen in the areas in which inflammation was present and were related in magnitude to the severity of the edema and interstitial infiltration. It is possible to assume that these T wave and ST-T segment changes are the consequence of anoxia due to an increase in the interstitial volume by the presence of edema and infiltration with a

resulting impairment of oxygen diffusion.[22,24]

Degenerated myocardial fibers are eventually replaced by fibroblastic proliferation so that fibrosis is to be found in the inflammatory foci, whereas the myocardial tissue between these foci remains healthy. This explains the fact that, in most cases *S. cruzi* produces a disseminated focal myocarditis and later a patchy fibrosis.

The *T* wave and *ST-T* segment changes as well as the degeneration of myocardial fibers have been attributed to coronary vascular lesions.[8,9,10] In some clinical papers[17] the ECG findings in Chagas myocarditis have been compared to those in arteriosclerotic coronary disease. Conversely, coronary damage has been reported in some experimental and histopathologic studies of Chagas myocarditis.[8-10] No evidence of coronary damage has been found in this series of experiments, or in some others.[3,26] Gore[27] has pointed out the reversible nature of the ECG changes in many cases of myocarditis and on this basis, rules out coronary damage[5,8-9] or destruction of small blood vessels[19] as their cause. Furthermore, Scherf and Boyd[28] and Dias and associates[14] have described ECG changes that appear and disappear alternately in relation to large inflammatory areas in the heart muscle. These same changing abnormalities were observed in the daily tracings obtained in our dogs. QS complexes like those seen in myocardial infarction were observed over areas of subepicardial or full-thickness fibrosis, mainly where this fibrosis was so abundant as to give rise to confluent areas of scar tissue. These areas are, electrophysiologically, like the areas of necrosis in a myocardial infarction.

Conduction disturbances may be observed at discrete points on the lateral surface of the ventricles (local blocks) and at these same points diffuse infiltration, degenerated and atrophic muscle fibers, and fibrosis are usually found. Unipolar leads at these points show polyphasic ventricular complexes, predominantly positive, such as those seen in bundle branch block. In Fig. 9 the tracing from point *A* is an example. It resembles a RBBB tracing, but is obviously not one since the unipolar leads at *C* and *D* are predominantly negative (QrS and QS). Since there is dense transmural fibrosis at these latter points, the corresponding ventricular complexes should be predominantly positive if RBBB exists, as has been proved experimentally.[29] We can conclude that the RBBB-like polyphasic complexes observed are produced by local conduction disturbances at the site of myocardial inflammatory process.

Summary

The effects of a highly virulent strain of *Schizotrypanum cruzi* (*S. cruzi*) on 72 pups have been studied. Histologic abnormalities compatible with the diagnosis of myocarditis were found in 87.1 per cent of the 31 surviving dogs. Electrocardiographic abnormalities were present in 74 per cent. This correlation proves the great value of the electrocardiogram in the diagnosis of myocardial damage.

Circulating forms (trypanosomes) of *S. cruzi* were found frequently during the acute stage of the disease, but as was shown, their absence does not rule out the existence of infection. There was no correlation between the number of parasites in the blood and the severity of histologic lesions in the heart.

The correlation between unipolar epicardial ECG tracings and histologic findings in the same areas was analyzed. The observation was that T wave and ST-T segment changes are registered over inflammatory foci and that the magnitude of these changes is proportional to the amount of edema and the density of the interstitial cellular infiltration.

The manifestations of acute Chagas heart disease do not differ essentially from those due to acute myocarditis of other etiologies. It is proved that the histologic abnormalities are due to impaired oxygen diffusion as a consequence of edema and cellular infiltration which expand the interstitial space.

S. cruzi produces a multifocal myocarditis that eventually leads to fibrosis, through circumscribed anoxia as a consequence of inflammatory foci.

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Effects of glyceryl trinitrate and pentaerythritol tetranitrate on forelimb, renal, mesenteric, and total peripheral resistances

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Vasodilation has yet to be demonstrated conclusively for the commonly used pharmacologic agent, pentaerythritol tetranitrate† (PETN). The ability of organic nitrates, especially glyceryl trinitrate (GTN), to produce marked vasodilation of peripheral vascular beds, however, is well known.[1] Because of the insolubility of PETN, acute hemodynamic investigations of the drug were limited to those observations obtained after oral administration of it.[2] Oral administration has several disadvantages, including the extreme variability of drug absorption and the necessity of measuring drug effects at one particular time without taking into consideration the highly variable time delay due to absorption.

A soluble preparation of pentaerythritol tetranitrate dissolved in polyethylene glycol-400 (PEG) has recently become available, thereby making it possible to determine more reliably acute vascular changes. This study was designed, therefore, to compare the immediate effects of GTN and PETN on systemic hemodynamics, as well as on the constantly perfused forelimb, kidney, and mesenteric circulations of the dog.

Methods

The study included a total of 48 mongrel dogs of both sexes, whose weights averaged 15.6 kilograms. The animals were anesthetized with pentobarbital sodium (35 mg. per kilogram); heparin sodium (5 mg. per kilogram) was used as the anticoagulant.

Systemic hemodynamics. Two polyethylene catheters were introduced through the right and left femoral veins into the right atrium and ventricle, respectively. These catheters were connected to a multiple stopcock arrangement which was attached to a Statham pressure transducer. In this manner, right atrial and ventricular pressures were recorded on a direct-writing

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†Generously supplied by Dr. James Weir, Warner-Chilcott Laboratories, Morris Plains, N.J.

multichannel oscillograph. Another catheter was inserted through the right external jugular vein into the superior vena cava, thereby providing the site for injection of the pharmacologic agents. The right carotid artery was cannulated with polyethylene tubing attached to a second Statham pressure transducer for continuous recording of systemic arterial pressure. A fifth cannula was inserted through the right femoral artery into the abdominal aorta and connected to a Waters cuvette and densitometer and infusion withdrawal pump. A precalibrated Sigmamotor pump was interposed between another cannula introduced through the left femoral artery into the aorta and the left brachial artery. In this manner the flow of blood to the left forelimb was held constant and changes in arterial perfusion pressure were recorded by the attachment of a third Statham pressure transducer to a needle inserted just proximal to the perfusion cannula. Average blood flow in the forelimb was 71 ml. per minute for the 13 animals studied by this technique. It is possible that changes in aortic pressure may have modified the flow of blood into the limb through collateral circulation at the shoulder. Under these circumstances, measurements of resistance may not be precise; however, since aortic pressure remained unchanged in the local infusion experiments (*vide infra*), the observations made in this series of animals seem to be valid. A schematic diagram of the experimental set-up is presented in Fig. 1.

Cardiac output was calculated by means of the Stewart-Hamilton formula[3,4] using indocyanine green dye. One bolus of the dye (3 mg.) was injected into the right ventricle (using a precalibrated syringe) and this was then followed immediately by an injection of 5 ml. of normal saline; both syringes were attached to the same three-way stopcock. The dye curves were obtained by withdrawing arterial blood through the cuvette with the constant-speed pump attached to a Servo-recorder. After the recording of each curve, the withdrawn blood was reinfused.

Total peripheral resistance was calculated by dividing the systemic vascular pressure gradient (difference between carotid arterial and right atrial pressures) by the calculated cardiac output. Since forelimb venous pressure was not measured, changes in forelimb vascular resistance were estimated by dividing the brachial arterial perfusion pressure by the blood

Fig. 1. Schematic diagram of the experimental set-up for the studies of systemic hemodynamics.

flow Both resistance values are expressed as millimeters of mercury per milliliter per minute (mm. Hg/mL/min.)

Glyceryl trinitrate (powder) and pentaerythritol tetranitrate (in polyethylene glycol-400) both were brought to a concentration of 100 μGm per milliliter in isotonic saline and were given intravenously to 10 and 8 dogs, respectively in a dosage of 10 μg per kilogram Hemodynamic measurements were made immediately before administration of the drug and then at 1.5 5 and 10 minutes after injection. Since PETN is dissolved in PEG equal volumes of this solution were also given (8 dogs)

Forelimb vascular preparation The left forelimb of 10 additional dogs was prepared for constant perfusion using the technique of Haddy and associates.[4] A blood pump was interposed between the left femoral and brachial arteries. Large artery perfusion pressure was measured by inserting a needle into the perfusion tubing just proximal to the cannula a small artery and vein in the foot pad were cannulated and a needle was inserted into the large cephalic vein for the measurement of pressure in these vessels Systemic arterial pressure was measured from another cannula inserted through the right femoral artery into the abdominal aorta. Pressures were recorded by an attachment of the Statham pressure transducers to a multichannel oscillograph By the calculation of the pressure gradients between the large and small arteries, large and small veins, the small artery and small vein and the large artery and large vein, and the division of each by the blood flow resistances could be determined for the arterial venous small vessel and total vascular segments, respectively Average forelimb blood flow for this group was 95 ml per minute GTN PEG and PETN in the same concentrations used above were infused into the perfusion tubing upstream from the pump at the following rates 0.12 0.25 0.49 1.23 2.47 and 4.94 ml per minute in that order Each rate was maintained for 30 seconds as all pressures were recorded

Mesenteric vascular preparation The superior mesenteric vascular bed of 12 dogs was perfused at a constant blood flow by interposing the blood pump between the left femoral and superior mesenteric arteries. Pressures were measured and recorded in a manner similar to that described for the forelimb This technique was presented in detail in a previous communication.[4] Large artery pressure is mesenteric artery perfusion pressure the small artery and vein pressures were measured from cannulated branches of small mesenteric vessels approximately 5 cm from the intestinal border large vein pressure was measured from a branch of the portal vein Mesenteric vascular segmental resistances were calculated from pressure gradients for the arterial venous small vessel and total vascular segments divided in each case by the blood flow Systemic arterial pressure was recorded from a catheter inserted into the aorta through the contralateral femoral artery The three solutions were infused into the perfusion tubing upstream from the pump, for 30 seconds each at the same rates and concentrations used for the forelimb preparation

Renal vascular preparation The right kidney of 13 dogs was perfused at a constant blood flow by interposing the pump between the right femoral and renal arteries. The preparation was described in an earlier communication The average renal blood flow was 110 ml per minute Systemic and renal arterial perfusion pressures were measured from a cannulated left femoral artery and the renal artery perfusion tubing using two Statham pressure transducers attached to the oscillograph. Even though renal vein pressure was not measured, an index of vascular resistance was obtained by dividing the perfusion pressure by blood flow Each agent was infused into the perfusion tubing upstream from the pump at the same concentrations and rates and for the same time duration used with the forelimb and mesenteric circulations.

Results

Systemic hemodynamics. Table I summarizes the studies comparing the effects of GTN PEG and PETN on forelimb and total peripheral resistances and cardiac output After injection of PEG there were no significant changes in cardiac output

Table I Per cent change (from control) in total peripheral resistance forelimb resistance, and glycol-400 and pentaerythritol tetranitrate

	Mean arterial pressure			*Total peripheral resistance*		
	1.5 min	*5 min*	*10 min*	*1.5 min*	*5 min*	*10 min*
Glyceryl trinitrate (10 dogs)						
Mean	−25	−12	−13	−18 3	−1 6	−5 2
S.E.	2 5	2 2	2 2	6 5	3 3	3 6
p<	001	001	001	02	80	20
Polyethylene glycol-400 (8 dogs)						
Mean	−3	−4	—	−11 12	−9 8	—
S.E.	2 2	4 8	—	4 80	5 0	—
p<	20	40	—	10	10	—
Pentaerythritol tetranitrate (8 dogs)						
Mean	−8	−6	−8	−11 5	−5 4	−6 6
S.E.	1 8	1 9	1 9	2 0	2 6	3 0
p<	01	01	01	001	10	10

Indicates statistical significance at least at the 5 per cent confidence level

heart rate and aortic, right atrial and forelimb perfusion pressures. Total peripheral and forelimb vascular resistances, therefore, remained unchanged with the vehicle for PETN

Cardiac output did not change significantly after equal dosages (by weight) of GTN and PETN thus, the decreases in aortic and forelimb arterial pressures after injection of these agents were produced by the significant decreases in total peripheral and forelimb vascular resistances, respectively Mean aortic pressures were 100 76 88 and 83 mm Hg at 0 1.5 5 and 10 minutes, respectively after injection of GTN and 97 and 91 mm Hg respectively after inj[illegible] PETN Forelimb vascular resistanc[illegible] 1 5 5 and 10 minutes after GT[illegible] PETN were [illegible] 28 2.64 and [illegible] mm Hg per milliliter per minute, and 2 59 49 2 49 and 2 53 mm Hg per milliliter per minute, respectively A significant decrease in total peripheral resistance was observed only at 1 5 minutes after both organic nitrates but only with PETN did significant forelimb dilation persist for 5 minutes.

Forelimb circulation. The effects of GTN and PETN and their respective solvents on pressures and segmental vascular resistances are shown in Fig 2 The data pre[illegible] the control for

GTN were taken from a previous repor[illegible] and demonstrate that the infusion [illegible] isotonic sodium chloride has no signific[illegible] effect on the segmental resistances in [illegible] dog forelimb Isotonic GTN (100 [illegible] per milliliter however markedly [illegible]creased forelimb vascular resistance infusion rates as low as 12 μGm per min[illegible] by reducing small vessel segmental re[illegible]tance. The responses with PETN [illegible] GTN were qualitatively similar quant[illegible]tively the changes with PETN were [illegible] At the lowest infusion rate (12 μGm[illegible] minute) total and small vessel segm[illegible] resistances decreased 6 and 10 per [illegible] respectively with GTN and 1 and [illegible] cent respectively with PETN Sim[illegible] at the highest infusion rate (0 49 m[illegible] minute) tot[illegible] and small vessel res[illegible] decreased 34 and 40 per cent respec[illegible] with GTN and 27 and 37 per ce[illegible] spectively with PETN The vaso[illegible] observed with PETN may not be [illegible]tirely to the nitrate, since PEG the[illegible] produced a fall of 8 per cent in to[illegible] and small vessel segmental resist[illegible] the highest infusion rate. Heart [illegible] highest infusion rate the approx[illegible] falls in total and small vessel re[illegible] with PETN were 15 and 25 per ce[illegible] spectively whereas GTN pro[illegible] spective decreases of 24 and [illegible]

cardiac output at 1.5 5 and 10 minutes after injection (IV) of glyceryl trinitrate polyethylene

Forelimb resistance			Cardiac output		
1.5 min.	5 min.	10 min	1.5 min	5 min	10 min
−13 5	−1 1	−1 2	−5 1	−7 7	−4 8
2 7	1 5	2 2	5 7	5 3	5 6
001	90	60	40	20	50
−0 9	−2 5	—	−10 6	+7 9	—
0 8	3 0	—	6 7	6 4	—
20	50	—	20	30	—
−3 9*	−3 7	−2 0	+3 5	−0 2	−0 1
1 1	1 4	1 0	2 5	2 8	4 4
01	05	10	20	> 90	> 90

Mesenteric circulation The responses of the superior mesenteric vascular bed were different from those obtained in the fore limb, and are presented in Fig 3 The isotonic sodium chloride data are taken from an earlier communication [9] and demonstrate that the control for GTN has no effect on the segmental resistances of the mesenteric circulation. GTN produced decreases in total arterial and small vessel resistances venous resistance did not change. At the highest infusion rate GTN decreased total and small vessel resistances 26 and 58 per cent, respectively whereas PEG and PETN at the same infusion rate, decreased these segmental resistances by 18 and 20 per cent and 16 and 58 per cent, respectively Hence, the dilation observed with PETN in the mesenteric vascular bed may be attributed primarily to its vehicle, PEG The resistance data (Fig 3,B) suggest that dilation of small vessels occurs with PETN at low doses whereas, at these same infusion rate, PEG has no effect.

Renal circulation The changes observed in the renal vasculature during infusion of each solution were similar to the responses obtained in the mesenteric circulation (Fig 4) The sodium chloride infusion reported earlier [7] produced no response in the renal vasculature in contradistinction to GTN Both PETN and PEG produced renal vasodilation but there were no differences in the responses to the nitrate and its vehicle. With the lower infusion rates these latter two solutions produced increases in renal vascular resistances.

The results for the calculated small vessel resistances of the forelimb and mesenteric vascular beds and the total renal vascular resistance are presented in Table II

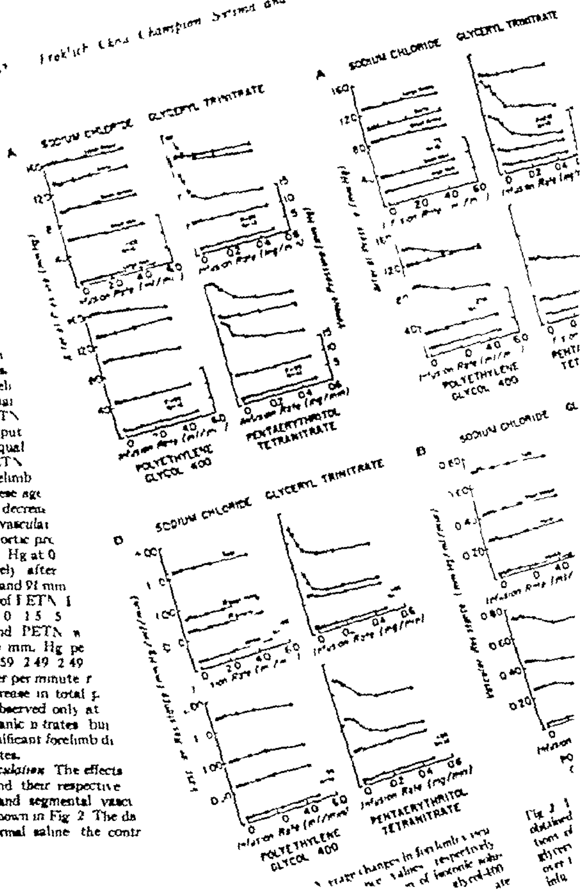
Discussion

The results of this study demonstrate that both GTN and PETN when administered intravenously actively decrease vascular resistance in both the systemic circulation and the constantly perfused dog forelimb Since equal amounts by weight of each agent were given an approximation of the vasodilating potency may be made by comparing the respective changes in resistance produced by these drugs. The systemic hemodynamic studies suggest that GTN is approximately 1.5 times as potent as PETN on calculated total peripheral resistances, and 3 times as potent on forelimb vascular resistance. Since cardiac output and forelimb blood flow remained unchanged coincident with the fall in systemic arterial and forel fusion pressures, the decreas

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utes respectively after
and 97, 89, 92, and 91 mm
after injection of PETN. I
resistances at 0, 15, 5
after GTN and PETN w
2.64 and 2.56 mm. Hg pe
minute and 2.59, 2.49, 2.49
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PETN did significant forelimb di
ast for 5 minutes.

Forelimb circulation. The effects
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Table II Changes in calculated small vessel resistance (R_{SV}) in the forelimb and mesenteric circulations and total renal vascular resistance (R_T) as a function of increasing infusion rates of glyceryl trinitrate (GTN) and pentaerythritol tetranitrate (PETN)

	Infusion rate (mg./min.)						
	0	0.012	0.025	0.049	0.123	0.247	0.494
Forelimb (mm. Hg/ml./min.)							
GTN—R_{SV}	1.06	0.96	0.81	0.73	0.64	0.65	0.60
S.E.	0.16	0.16	0.08	0.14	0.13	0.12	0.10
PETN—R_{SV}	1.08	1.06	1.04	0.99	0.82	0.74	0.68
S.E.	0.15	0.15	0.15	0.15	0.14	0.14	0.12
Mesenteric (mm. Hg/ml./min.)							
GTN—R_{SV}	0.38	0.36	0.35	0.32	0.22	0.19	0.16
S.E.	0.08	0.08	0.08	0.08	0.04	0.04	0.03
PETN—R_{SV}	0.43	0.42	0.42	0.42	0.40	0.37	0.33
S.E.	0.06	0.07	0.06	0.07	0.06	0.06	0.06
Renal (mm. Hg/ml./min.)							
GTN—R_T	1.28	1.23	1.15	1.08	1.00	0.90	0.84
S.E.	0.18	0.16	0.16	0.14	0.12	0.12	0.09
PETN—R_T	1.29	1.34	1.32	1.25	1.23	1.22	1.14
S.E.	0.13	0.14	0.16	0.13	0.16	0.17	0.21

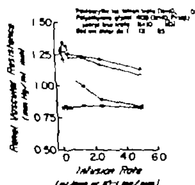


Fig. 4. Average changes in calculated renal vascular resistance after 30 seconds of infusion over the range of 0.01 to 0.49 mg. per minute. Each curve represents the average change in resistance obtained from 10 animals. Renal blood flow was 110 ml. per minute for each agent except sodium chloride.

lated vascular resistances must be explained by active increases in vessel diameter suggesting primarily arteriolar dilation. A longer duration of action of PETN is suggested from these data since significant forelimb dilation persisted for 5 minutes whereas GTN produced vasodilation only at 1.5 minutes.

The regional circulation perfusion studies were of interest since they showed differences between the two organic nitrates. GTN consistently dilated each perfused circulation; however, PETN failed to demonstrate significant mesenteric and renal vasodilation although forelimb dilation was observed. This information suggests that a long acting vasodilator such as pentaerythritol tetranitrate may be of value in disease states such as peripheral arterial insufficiency since increased peripheral flow may be achieved without redistribution of blood flow from the splanchnic and renal vascular beds. Finally, these studies suggest that PEC itself is vasoactive.

Summary

1. The systemic and regional hemodynamic effects of glyceryl trinitrate (GTN) and pentaerythritol tetranitrate (PETN) were observed in 48 dogs anesthetized with pentobarbital.

2. After intravenous injection of these drugs (10 μg per kilogram) cardiac output, venous pressure, and heart rate remained unchanged, but systemic and brachial arterial perfusion pressures decreased. The decrease in total peripheral and fo... were observed 1.5 min...

each agent forelimb vasodilation persisted for 5 minutes after PETN

3 Dose response curves were obtained with each agent after local infusion into the constantly perfused forelimb mesenteric and renal circulations. Dilation was always observed with GTN whereas PETN produced dilation only in the forelimb circulation

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Case reports

Ergotism due to therapeutic doses of ergotamine tartrate

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Food borne sporadic and epidemic ergot poisoning has been known for centuries and has been reported as recently as 1953.[3] Nowadays, however ergotism is more likely to arise from therapeutic use of ergotamine or ergotamine tartrate.[1-4,7,9,10] Compared to the extensive use of these drugs in thousands of patients all over the world there are but few reports of serious ergotism in the literature. Because of this fact and the rarity of radiographic confirmation of ergotism,[6,1] it seemed to be justifiable to report upon two cases recently observed at this hospital.

Case reports

Case 1 A 39-year-old housewife was admitted to Medical Department VIII in January 1963 as an emergency case because of arterial insufficiency in the lower extremities. She had suffered from migraine for more than 17 years, and had used ergotamine drugs (Cafergot comp. suppositories) during attacks for many years. Increased frequency of the migraine attacks had made the patient take ergotamine nearly every night for the previous 2 years. The first symptoms of arterial insufficiency in the lower extremities had started 5 years before and claudication had increased during the last 2 years, until, finally she could walk only a few steps without having pains. At the same time she noticed coldness of the feet. Except for two attacks of temporary vasospasm in her fingers on exposure to cold, she had no symptoms in the upper extremities. For 2 or 3 years she had shown some nervous disturbances.

In 1954 and 1958, she had had spontaneous abortions. In 1955 she had an uncomplicated delivery of a healthy child at expected term.

On admission, the legs were pale and cool. There were faint arterial pulsations in the groins [illegible] other arterial pulsations could be felt in the lower extremities. Pulsations in the radial arteries were reduced but otherwise there was no sign of arterial insufficiency in the upper extremities. The blood pressure in the upper extremities was 130 [illegible] Hg. The temperature of the skin of the [illegible] 20.4 to 21.5° Celcius.

OSCILLOMETRY At the level of the [illegible] was complete absence of oscillations [illegible] oscillations were present in the thigh [illegible] (Fig. 1).

ARTERIOGRAPHY The aorta and [illegible] were slender. The femoral arteries [illegible] narrowed, particularly in the dist[illegible] compensatory filling of large [illegible]

COURSE. Progressive improvement [illegible] drawal of ergotamine. After 5 [illegible] arterial spasm or arterial [illegible] A repeat arteriogram 9 days [illegible] normal findings (Fig. 3). The [illegible] in a healthy condition. Re[illegible] closed no symptoms of arter[illegible] her migraine has improved [illegible]

PROVOCATION TEST [illegible] after improvement of her [illegible] provocation test was [illegible] pository (containing 2 [illegible] given. After 3 hours, [illegible] lower extremities, [illegible] hours and lasting for [illegible] Sympathetic block [illegible] 72 hours [illegible] the level of [illegible] temperature of the [illegible] secretion of sweat [illegible]

From the Roentgen Department (Chief Prof. Dr. Med. J. [illegible]) and [illegible] Prof. Dr. Med. A. Jervell) Ullevål Hospital, Oslo, Norway
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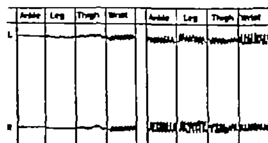


Fig. 1. Case 1. Oscillograph. *Left*, On admission. *Right*, Nine days after withdrawal of ergotamine. *L*, left, and *R*, right, lower extremities.

change in the arterial pulsation on the oscillogram. Intra-arterial injection of tolazoline 20 mg. and papaverine 60 mg. into the femoral artery did not influence the peripheral circulation.

In a second provocation test, ergotamine 1 mg. as suppository led to a minor degree of vasospasm. During this test no pathologic finding was detected by ophthalmoscopy, audiometry, or electroencephalography (EEG), or in renal blood flow as judged from inulin and PAH clearance.

Case 2. A 25-year-old married nurse was hospitalized in April, 1963, with a provisional diagnosis of embolism of the axillary artery. Because of severe and frequent attacks of migraine she had used ergotamine drugs (Cafergot comp. and Megergen) for at least 4 or 5 years. During the previous 2 months she had taken Cafergot comp. suppositories every day. The hands and feet had been cold for 4 years and for 3 years she had had typical claudication in the legs. During the last few weeks, persistent pains had occurred in the arms and legs during rest. She also had had some nervous disturbances for 3 years.

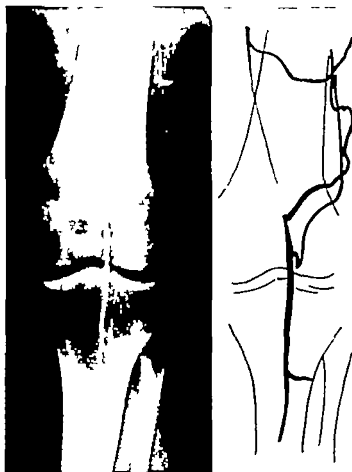


Fig. 2. Case 1. Arteriography on admission. Extensive spasm of the distal part of femoral artery. Compensatory filling of large collaterals.

On admission, there was evidence of arterial insufficiency in all four extremities, and this was most severe in the right hand, which was cold and cyanotic. No pulsation was felt in either the radial or ulnar arteries. Faint pulsation was felt in the axillary arteries. The arterial pulsation in the lower extremities was markedly reduced. The blood pressure in the upper extremities was not measurable.

OSCILLOMETRY. Very small oscillations were registered in the upper as well as in the lower extremities (Fig. 5).

LABORATORY FINDINGS. Electroencephalography revealed slight dysrhythmia on both sides, but otherwise the findings were normal.

ARTERIOGRAPHY. Arteriography was performed in the femoral artery. The right brachial artery was considerably narrowed, and the flow of blood to the arm was obviously reduced. The main branches from the axillary artery were also narrowed. There was compensatory filling of the lateral thoracic artery (Fig. 6). Similar findings were demonstrated in the large and medium-sized arteries of the lower extremities.

COURSE. Marked improvement in the arterial circulation followed withdrawal of ergotamine. Arteriographic examination 1 week later revealed practically no abnormal appearance of the arteries (Fig. 7).

A recent follow-up revealed that the patient had had an uncomplicated delivery of a healthy child in February, 1964. There were no symptoms or signs of arterial spasm and no symptoms of migraine. The electroencephalogram was normal.

Comments and discussion

The effect of ergotamine on the cardiovascular system is very complex.[4,8,9] Ergotamine has been shown to have a direct stimulating effect on the smooth muscle cell causing a vasoconstriction of isolated

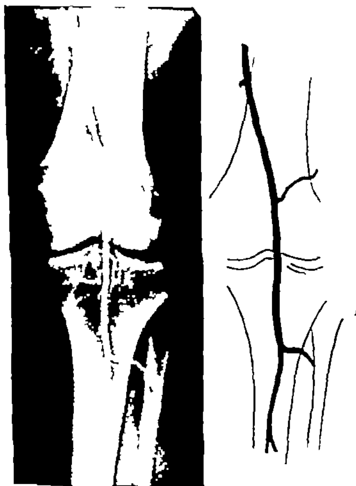


Fig. 7. Case 1. Arteriography 9 days after withdrawal of ergotamine. Normal findings.

main arteries and the collaterals is most probably due to a difference in the muscular layer of the vessels.

In our cases vasodilating drugs had no effect on ergotamine induced vasoconstriction. Sympathetic block led to increased temperature of the skin but there was no other sign of improved arterial flow to the extremity and no rise in arterial pulse volume. Therapeutic sympathetic block to relieve the vasoconstriction caused by ergotamine seems therefore to be of questionable benefit.

The nervous disturbances in our patients might have been due either to a direct effect on the central nervous system or to an effect on cerebral vessels. The electroencephalographic changes shown in one of the patients disappeared after ergotamine had been withdrawn.

Although ergotism is a rather well-known clinical condition, complications and side effects from ergotamine medication may be overlooked for years as happened in our patients. Every patient on ergotamine medication should be watched carefully for toxic manifestations and the possibility of hypersensitivity must be borne in mind. In patients with migraine ergotamine should be used intermittently only. Headache and nausea may be due to ergotamine intoxication and are in such cases often misinterpreted as symptoms of migraine.

Summary

Two cases of severe peripheral arterial insufficiency after the use of ergotamine suppositories are reported. Arteriography demonstrated severe spasm of the large and medium-sized arteries in the extremities with compensatory filling of collaterals. The symptoms disappeared completely after ergotamine had been withdrawn.

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Congenital aplasia of the myocardium of the right ventricle (Uhl's anomaly)

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Congenital aplasia of the right ventricular myocardium is of interest, not only as a rare congenital cardiac defect, but also as an experiment of nature that demonstrates the importance of right ventricular function. Since the report of Starr and associates[1] on the lack of any functional changes after cauterization of the canine right ventricle, controversy has arisen concerning the necessity of right ventricular contraction for the maintenance of a normal circulation. Congenital aplasia of the right ventricular myocardium produces a recognizable clinical syndrome and the resulting hemodynamic abnormalities suggest that the pumping action of the right ventricle is essential for normal blood flow.

Case report

M.A., a white girl, was admitted to hospital at the age of 7 months. She seemed to be weak and "not right" during the newborn period, and at the age of 3 months she became lethargic, developed frequent colds, and sweated at least once daily. Her color was dusky, only slight dyspnea was present, and the most notable feature was the weakness. On examination, the edge of the hard liver was felt 7 cm. below the costal margin. The brachial pulses were weak, the femoral pulses could not be felt. The heart rate was 190 and regular, the heart sounds were of very poor quality, the first sound was grossly diminished, and there was a presystolic gallop. A chest infection complicated the findings. There was only slight improvement after digoxin, diuretics, and oxygen.

The chest x-ray film (Fig. 1) showed a tremendously dilated heart with a cardiothoracic ratio of 9:14; the pulmonary vascularity was slightly diminished. The electrocardiogram (Fig. 2) showed a rate of 200 per minute, P-R of 0.09 second, QRS of 0.07 second, and low-voltage QRS complexes. The P waves in Lead II were 5.5 m[illegible], and 7.5 m[illegible] in Lead V_1, compared to a R wave of 2 m[illegible].

Heart catheterization studies (Table I) showed most unusual pressure curves in the right ventricle and pulmonary artery in that the major deflection was presystolic and due to atrial contraction, and the pulse contour was identical in the right atrium, right ventricle, and pulmonary artery (Fig. 3). The peak right atrial pressure was 5 mm. greater than the peak pulmonary arterial pressure. The arteriovenous oxygen difference was increased to 4.7 volumes per cent, and arterial oxygen saturation was decreased to 90 per cent by oximeter, with a pO_2 value of 54 mm. Hg. The arterial pCO_2 was decreased to 28 mm. Hg. In addition, systemic hypertension was evident.

The indicator-dilution curves from the left atrium and right atrium showed a marked contrast in contour (Fig. 4). The right atrial curve showed a small right-to-left shunt. From the right ventricle the appearance time was 6 seconds, and from the left atrium it was 2.5 seconds, but the big difference was in the mean transit times: 4.9 seconds from the

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Fig. 1. Posteroanterior and lateral chest x-ray films show dilated right heart and diminished pulmonary vascularity.

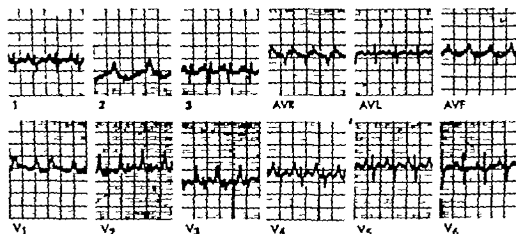


Fig. 2. Electrocardiogram. Sensitivity 1 mv = 10 mm. Paper speed, 25 mm. per second except for Leads II and V (50 mm. per second).

Table I. Heart catheterization data

Site	Oxygen saturation (%)	Pressure (mm. Hg)
Vena cava (average)	57	—
Right atrium	57	28/19
Right ventricle	57	23/14
Pulmonary artery	57	22/14
Left atrium	89	17.5/9
Femoral artery	90	160/100

left atrium and 22.0 seconds from the right ventricle to the femoral artery. The cardiac index was 1.75 L./min./M² for the right ventricular injection and 1.94 L./min./M² for the left atrial injection.

A selective angiocardiogram, with injection into the right atrium, showed a large dilated right atrium and right ventricle, and at 7 seconds the pulmonary filling was still poor and no filling of the left side of the heart was evident (Fig. 5). The lateral views (Fig. 6) showed a trace of right-to-left shunt through the foramen ovale.

The dilated right ventricle showed only fine trabeculation along the inferior and apical margins. The right atrium showed only a slight change in contour during atrial systole, the most notable change being in the appendage (Fig. 7). The right

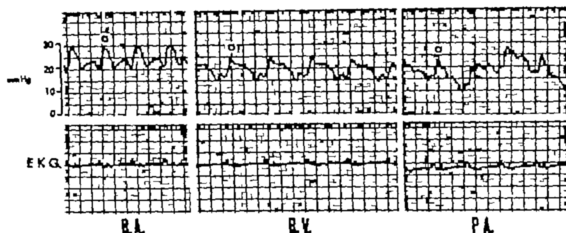


Fig. 3. Pressure curves. The "a" wave is peak pressure in the right atrium right ventricle, and pulmonary artery

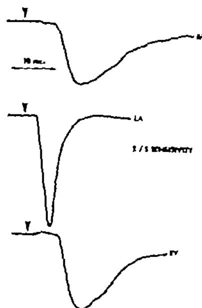


Fig 4 Indicator-dilution curves. *Top* RA injection, small right-to-left shunt. *Middle:* LA injection, recorder sensitivity reduced to two fifths. *Bottom* RV injection.

ventricular shape ltered only slightly during systole nd the decrease in the frontal area was small, but paradoxical pulsation was not evident

The diagnosis rested between Ebstein's disease with a parchment-like right ventricle and plasia of the right ventricular myocardium. Because of the rarity of the latter disease the diagnosis of Ebstein's disease was considered to be most likely

At operation the superior vena ca was anastomosed to the pulmonary artery and a patent anastomosis was effected. The heart stopped suddenly shortly after the operation was concluded and resuscitation was ineffectual.

At autopsy the heart weighed 48 grams (normal 38 grams) the right atrium and right ventricle were severely dilated. The tricuspid valve ring was 7 cm. in circumference (normal 4 cm) the leaflets were thin and normally attached to the annulus. Anteriorly the right ventricular myocardium was replaced by fibrous tissue, with sparse muscular elements at the pulmonary ring and diaphragmatic surface. The circumferences of the aortic, pulmonary and mitral valves were respectively 3.5 3.5 and 4.0 cm. (normal range). The left atrium and left entricle were grossly normal the ductus was closed. There was minimal probe patency of the foramen ovale. The free wall of the right ventricle measured 1.5 mm in thickness, and microscopy showed a thickened endocardium, some increase in elastic fibers, and just a few islands of myocardial cells with phyknotic nuclei, and pale cytoplasm with acuolar degeneration. The left ventricle was normal histologically Distribution of the coronary arteries was normal.

Discussion

Aplasia of the right ventricular myocardium is a rare disease. Four well-documented cases are to be found in the literature the initial case of Uhl,[1] 2 cases reported by Gasul and associates[3] and 1 case of Taussig[4] Less complete forms have been described as *parchment heart* a name originating with Osler Osler's case apparently involved both ventricles, and some normal myocardium was present. Another example[5] was that of a woman dying at age 24 the heart showed extreme dilatation of the right ventricle and with the right ventricle being on



Fig. 5. Angiocardiograms, posteroanterior view, right atrial injection. *Left*. At 1.5 seconds, right atrium filled, right ventricle filling. *Center*. At 3 seconds, right ventricle filled, early opacification of pulmonary artery. *Right*. At 7 seconds, medium still in right side of heart, decreased size of pulmonary arteries, central and peripheral.

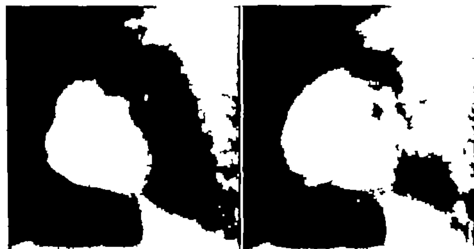


Fig. 6. Lateral angiocardiograms. *Left*. At 1.8 seconds, small shunt through foramen ovale. *Right*. At 7 seconds, small pulmonary artery, filling of left side has not yet occurred.

thick in places. The patient described by Reeve and MacDonald[6] died at age 47 of a subarachnoid hemorrhage. Cyanotic heart disease had been clinically evident from adolescence, and autopsy showed large areas in the right ventricle devoid of muscle fibers. The large dilated right ventricle of these patients is in contrast to the diminutive right ventricle found in patients with congenital hypoplasia of the right ventricle. In this anomaly the right ventricular wall is normal or increased in thickness.[7]

The clinical findings in the cases reported by Arcilla and Gasul[5] and in the present case are similar and distinctive. Heart failure commenced in infancy, the heart sounds were of poor quality, and precordial action was diminished despite marked cardiomegaly. No murmurs were evident; gallop rhythm was present.

The electrocardiograms showed marked right atrial hypertrophy and absence of normal right ventricular activity, and the chest x-ray films showed tremendous dilatation of the right atrium and the right ventricle with diminished pulmonary vascular markings. Angiocardiograms revealed marked right atrial and right ventricular dilatation, with loss of right ventricular

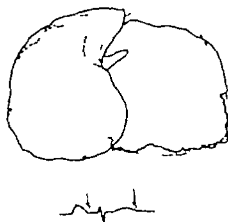


Fig. 7. Outline of right atrial and right ventricular contours on the angiocardiograms at the end of atrial systole (*dotted lines*) and ventricular systole (*solid lines*). Timing of films with respect to ECG is shown.

trabeculation and contractility and marked slowing of the circulation.

The pressure curves in our patient showed that the main force propelling blood through the lungs was right atrial contraction since the peak pressure wave in the right ventricle, right atrium and pulmonary artery was the "a" wave. In the case reported by Arcilla and Gasul[9] the right atrial "a" wave was transmitted to the right ventricle and pulmonary artery but ventricular contraction still produced the largest pressure wave. Their patient also had elevation of left atrial pressures, presumably due to endocardial fibroelastosis affecting the left ventricle.

Congenital aplasia of the right ventricle presents a distinctive clinical syndrome and only Ebstein's disease of the tricuspid valve should give difficulty in the differential diagnosis. This differentiation may not be possible for Ebstein's disease may be associated with a parchment-like change in the right ventricle with marked attenuation of right ventricular contractility. Taussig[4] described a patient in whom the clinical and hemodynamic findings resembled those of hypoplasia of the right ventricle and in whom autopsy eventually showed Ebstein's malformation. One of us has also observed a patient with Ebstein's disease who had a parchment-like right ventricle with almost similar pulse contours in the pulmonary artery, right ventricle and right atrium. The angiographic demonstration of displacement of a tricuspid valve cusp may be inconclusive in obvious cases of Ebstein's disease and a displaced cusp was considered to be a possibility in the angiocardiogram of our patient.

Intracardiac electrocardiography was not performed in our study. The typical finding in Ebstein's disease is the presence of right ventricular electrical potentials with a right atrial pulse contour when the catheter lies in the inflow region of the right ventricle. Since the pulse contour of the entire right ventricle was similar to that of the right atrium in our patient, this finding would not have been helpful. However, the absence of any right ventricular contribution to the right ventricular intracavitary ECG might be helpful in the recognition of fibrous replacement of the myocardium of the right ventricle.

Starr and associates[1] found no elevation of venous pressure after extensive cauterization of the canine right ventricle. Bakos[9] repeated this work and found no change in pulmonary arterial or systemic venous pressures and concluded that an actively functioning right ventricle was not absolutely necessary. In this work destruction of the free right ventricular wall seemed to be complete, as judged by autopsy examination and by the absence of right ventricular electrical activity and the lack of visible contraction. Donald and Essex[10] confirmed these findings; only a slight elevation of inferior vena caval pressure was observed after right coronary artery ligation, although in some animals the venous pressure curves were suggestive of tricuspid regurgitation. Bakos[9] suggested that tension of the left ventricular muscle mass has sufficient mechanical effect on an inert right ventricular muscle mass to maintain pulmonary arterial pressure.

However, subsequent attempts to bypass the right ventricle by anastomosing the right atrium or vena cava to the pulmonary artery in both acute and chronic experiments have resulted in failure. After creation of the anastomosis, clamping of the right ventricular outflow area produced an abrupt fall in pulmonary art

and systemic pressures.[11] In chronic studies,[12] anastomosing of the inferior vena cava to the pulmonary artery led to ascites and elevation of venous pressure whereas the creation of an anastomosis of the superior vena cava to the pulmonary artery was well tolerated despite an elevated venous pressure. The latter procedure is now the method of choice in the treatment of selected cyanotic congenital heart malformations especially tricuspid atresia.[13]

These bypass experiments conclusively demonstrated that venous pressure alone is unable to maintain a normal pulmonary blood flow indefinitely without the production of symptoms—at least in the dog. This does not refute Bakos' theory since the effect of the left ventricle on right ventricular function was eliminated by these bypass experiments.

In our patient with congenital absence of the right ventricular myocardium right ventricular contraction as judged by ventricular pulse contour was absent. Left ventricular contraction did not produce adequate emptying of the right ventricle and did not maintain pulmonary arterial pressure. This however may be due to the tremendous dilation of the right ventricle that is absent in acute experimental studies. Thus, although it is possible that the destruction of the right ventricle was not complete as the experimental reports suggest, the animal and clinical findings are not necessarily incompatible.

The creation of an anastomosis of the superior vena cava to the right pulmonary artery is the procedure of choice in patients in whom the normal pumping action of the right ventricle is seriously impaired. The improvement produced by this procedure is easy to understand in patients with tricuspid atresia. In patients with Ebstein's disease or aplasia of the right ventricle no obstruction to blood flow is present, and the main action of the bypassing of the right ventricle would seem to be the elimination of an excessively large venous reservoir.

Summary and conclusions

Total aplasia of the right ventricular myocardium was found in an infant with marked cardiomegaly and heart failure. Hemodynamic studies showed absence of right ventricular contraction and the peak pulse wave in the right ventricle was the right atrial a wave. Death followed attempted creation of an anastomosis of the superior vena cava to the right pulmonary artery.

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The metabolism of hypertension

Its relation to drug therapy

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The treatment of hypertension can only be understood in the light of knowledge of physiologic and metabolic derangements in the various types of hypertensive disease. Some of this knowledge is incomplete but enough is available to justify this effort to place various therapies of the hypertensive diseases in their proper frames of physiologic and metabolic reference. The major divisions of the discussion will be (1) neural function and catecholamine metabolism, (2) electrolyte, hormone, and tissue metabolism, and finally, (3) the action of drugs. In addition, the known connecting links between various systems will be defined and a table presented to show how blood pressure is raised in various hypertensive states.

Neural function and catecholamine metabolism

Some catecholamine is synthesized in chromaffin tissue, such as the adrenal medulla, but most is synthesized in the sympathetic nervous system.[1] The starting substance is the amino acid L-phenylalanine which is converted by a hydroxylase to L-tyrosine.[2] The latter can also be taken up by the blood and is converted by L-tyrosine hydroxylase to L-dopa (D). This is the rate-limiting step.[3] Further steps are D to L-dopamine (DA), DA to L-norepinephrine (NE), and NE to L-epinephrine (E). E and NE are stored, the former in chromaffin tissue and the latter in both chromaffin tissue and in certain neurones, including the sympathetic nerves.[4] The storage complex contains adenosine triphosphate (ATP) and a protein (Fig. 1) in vesicles or granules.

The neural storage mechanism can store not only locally synthesized but also circulating catecholamines,[6] as well as structurally related substances,[7] and can also re-store a portion of the catecholamines released from their granules.[8] This release is achieved in the sympathetic nerves by neural firing or discharge, the pathways for which are illustrated in Fig. 2. Sensory stimulation as well as sensory inhibition of this system probably involves innumerable pathways, but the chief autonomic inhibition takes place in the vasomotor centers of the brain stem from vasosensitive areas, such as the carotid sinus, pulmonary and

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Review

The metabolism of hypertension

Its relation to drug therapy

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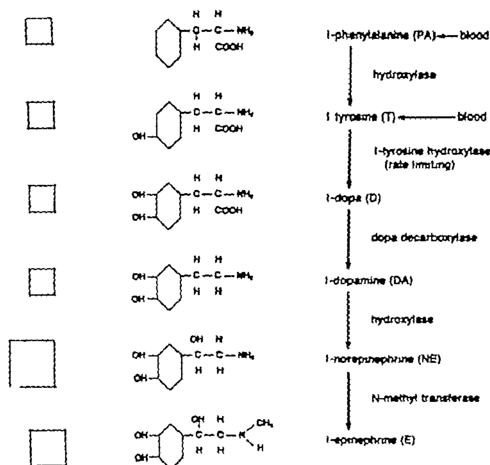


Fig. 1. Synthesis of catecholamines. The store consists of a complex in granules of NE and/or E with adenosine triphosphate (ATP) and other substances. Most synthesis takes place in the sympathetic nervous system, which stores only NE. The remainder takes place in chromaffin tissue including the adrenal medulla, which stores mostly E and some NE.

cardioaortic areas.[9] These baroreceptors or modulators defend the body against rises (or falls) in blood pressure.[10] It has been postulated from animal studies that in hypertension they become relatively insensitive to an increase in pressure and are "reset" for action at higher levels of blood pressure.[1]

As the catecholamines are released for α and β receptor stimulation[11] they are quickly degraded by enzymes, the pathways for which are shown in Fig. 3. The chief enzymes involved are catechol-O-methyl transferase (COMT)[12] and monoamine oxidase (MAO)[13,14] and the chief metabolites are normetanephrine (NM), metanephrine (M), 3-methoxy-4-hydroxyphenylethylglycol (MHPG), 3,4-dihydroxymandelic aldehyde (DPA), and vanillyl mandelic acid (VMA).[15-17] Some of these metabolites are conjugated in the liver to form sulfates and possibly glucuronides, and most of them, as well as E and NE, can be detected in the urine and blood under certain circumstances.[18,19]

Modern tests for pheochromocytoma depend on the detection of increased amounts of these metabolites in the urine.[20] Four such tests are currently used by us. Two tests were developed in our laboratory and two in other laboratories. They include the chromatoelectrophoretic assay for the catecholamine metabolites (CM), NM, M and NMG (CM test) (Wolf),[21] the VMA screening test (Gitlow),[22] the metanephrines to vanillin spectrophotometric test (Pisano),[24] and the bidirectional paper chromatographic VMA test (Armstrong)[25-27] in the

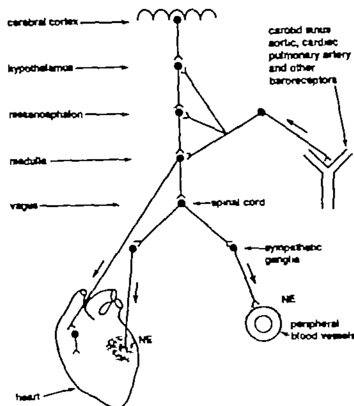


Fig. 2. Neural pathways for vasoconstriction and vasodilatation and cardiac stimulation and inhibition (Note that the weak cholinergic outflow to blood vessels is omitted i the diagram.)

order of their sensitivity and simplicity. In doubtful cases, all of these as well as other tests may be needed.

In pheochromocytoma catecholamine metabolism is deranged. Synthesis is increased[7,16] and the storage pool turnover rate is usually increased.[17] This can be demonstrated by studying the specific activities of urinary metabolites after administration of the tracer *dl*-β-H NE. The store of E and or NE is large in the tumor[16] and of NE, large in the sympathetic nervous system.[7] Evidence for this consists of direct assays of tumors and a positive tyramine test. Release from stores is increased as manifested by high plasma and urinary levels of NE and or E and their metabolites.[1,16,18,17,18,22] Degradation may be abnormal in that there may be a greater than normal ratio of amine to acid metabolites.[17]

Catecholamine metabolism is also abnormal in essential hypertension. Synthesis is probably normal as manifested by normal excretion of E, NE, and metabolites.[16] (Excretion is usually in balance with synthesis.) The store of NE is probably small and the storage mechanism impaired.[18] Evidence for this consists of increased disappearance rate of the stored tracer *dl*-β-H[3] NE in plasma from 3 to 24 hours after its administration[18] and increased vascular reactivity to infused NE in essential hypertension[14] and in prehypertensive children.[17] Release from the small store is probably normal although fluctuations from the mean are greater than normal[12] (effect of emotional states influencing catecholamine release from stores?). Diurnal release in contrast to nocturnal may be increased in essential hypertension.[17] The evidence for this is obtained from studies of urinary and plasma catecholamines and metabolites.[14]

Electrolyte hormone and tissue metabolism

The processes described in this section all participate usually as secondary but in some instances as primary mechanisms in hyper

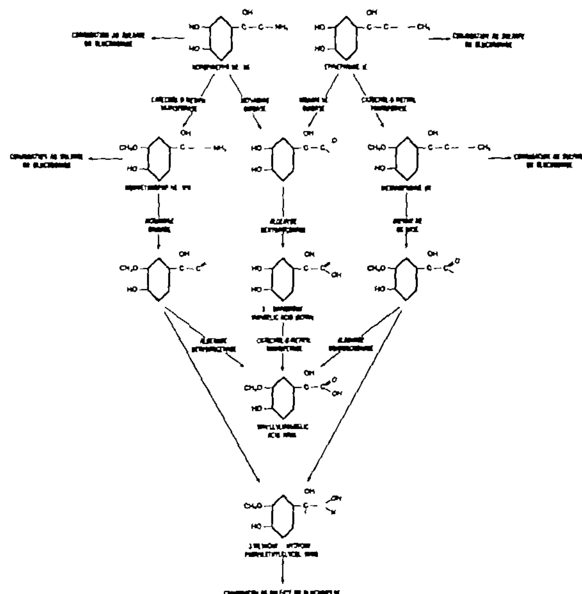


Fig 3 Degradation of catecholamines.

tension They are only partially understood The links between the systems and the manner in which blood pressure is raised in various types of hypertension are described in Tables I and II

The metabolism of sodium is still incompletely understood The ion is ingested and then transported in the blood to the extracellular fluid and the cells of all tissues. It is stored in many tissues, particularly bone and takes part in many metabolic processes.[39] It is intimately related to and influences the concentration and function of other ions, such as chloride potassium calcium, and magnesium [40] Many hormones influence the concentration and distribution of sodium such as the *mineralocorticoids, pituitary antidiuretic hormone* and others.[41] Sodium is excreted in a complex way largely by the kidney in which it is filtered by the glomeruli reabsorbed and possibly secreted by the tubules,[42] and influenced by a countercurrent mechanism [43] These functions are also governed in part by enzymes and hormones.[44] The ion is excreted partially in sweat and in the feces.[45]

Table I Known and suspected links between the known systems

1. Hereditary alteration in gene or genes influences the nature of the complex in the sympathetic neural storage granules (hypothetical)

2. Decreased ability to accept released NE back into small NE storage pool increases reactivity to infused NE (evidence suggestive). Emotional factors increase vasoconstriction by increasing free NE in this frame of reference

3. Norepinephrine and presumably any vasoconstrictive substance increases the concentration of sodium in the walls of the blood vessels

4. Increased concentration of sodium in the vascular walls increases reactivity to vasoactive substances

5. Increased reactivity to vasoactive and cardioactive substances increases vasoconstriction, with an increase in blood pressure and, possibly cardiac output in some cases

6. The carotid sinus and other baroreceptors defend the body against hypertension from any cause at first, but later become reset at higher levels (evidence incomplete)

7. Any increase in blood pressure can produce a further increase in the myogenic stretch reaction

8. Decreased stretch of kidney vessel receptors stimulates juxtaglomerular cells to produce renin (evidence suggestive)

9. Circulating angiotensin II and NE increase the blood pressure by producing direct vasoconstriction and cardiac stimulation. Angiotensin II enters norepinephrine storage pool (hypothetical). At any rate, there is a relationship between its action and sympathetic neural function

10. Secretion of aldosterone is stimulated by angiotensin II and ACTH and influenced by the depletion or retention of salt

11. Angiotensin II influences the excretion of sodium by the kidney independently of its effect on aldosterone

12. Aldosterone increases the retention of sodium by the kidney and the concentration of sodium in tissues

13. Juxtaglomerular apparatus is inhibited by aldosterone

14. Necrosis of afferent glomerular arterioles due to excessive vasoconstriction produces autoimmune reaction

15. Lipid and sterol metabolism is influenced by catecholamines (possible link with atherosclerosis)

16. Reduction in blood pressure decreases serum cholesterol and atherosclerosis in animals

17. Glucocorticosteroids increase vascular reactivity chiefly in normotensive subjects. Do they decrease NE storage pool (Hypothetical.) Decreased conjugation and abnormal catabolism of glucocorticosteroids and other steroids in essential hypertension. Also, decreased urinary excretion of pregnanetriol. If these defects result in more free glucocorticosteroid, reactivity to NE will be increased

18. Increased blood viscosity can increase peripheral resistance and blood pressure

19. Others which as yet are undiscovered

The mineralocorticoids, particularly aldosterone, are most important regulators of sodium metabolism. They are secreted by the zona glomerulosa of the adrenal cortex in response to stimulation by adrenal corticotropic hormone (ACTH)[4, •] or angiotensin II (AT).[47] Their secretion is also influenced either directly or indirectly by the depletion or retention of salt.[41] These corticoids are distributed by the blood to all of the tissues, including the kidney. In the tissues they influence the transport and distribution of ions, including sodium and in the kid[illegible] tend to stimulate reabsorption of [illegible] and promote the excretion of [illegible] They also inhibit the

Table 11 How the blood pressure is increased in hypertension

1 Direct stimulation by vasoactive substances, such as l-norepinephrine epinephrine or angiotensin II	1 Pheochromocytoma renovascular hypertension chronic renal and accelerated essential hypertension, iatrogenic
2. Decreased NE store Released NE cannot be readily accepted back into store and more is available for vasoconstriction This is the probable cause for increased vascular reactivity to infused vasoactive substances in early essential hypertension If the store is decreased further however by therapy no NE can be released by the nerve impulses, and the blood pressure falls The hereditary factor may be transmitted by a protein in the storage complex	2 Essential hypertension and prehypertension Cushing s syndrome
3 Accumulation of AT in NE store (hypothetical) AT is ten times as potent as NE	3 Renovascular hypertension accelerated essential hypertension
4 Decreased neural defense against hypertension by diminished activity of the carotid sinus and other baroreceptors for any given level of blood pressure	4 All hypertension? Eventually
5 Increased concentration of Na+ in smooth muscle and possibly in sympathetic nerves influencing concentration of other electrolytes and increasing reactivity to vasoactive substances also produces edema of blood vessels and, hence increased resistance	5 Accelerated essential hypertension chronic renal and renovascular hypertension primary and secondary hyperaldosteronism Any long-standing hypertension whatever the primary cause
6 Autoregulation. Increased blood pressure produces myogenic stretch reactive vasoconstriction potentiating hypertension	6 All hypertension eventually
7 Constriction of main renal artery or branch, with stimulation of renin-angiotensin-aldosterone system	7 Renovascular hypertension, malignant nephrosclerosis? Chronic glomerulonephritis And other forms of renal hypertension?
8. Excessive secretion or administration of aldosterone and other mineralocorticoids	8 Aldosterone producing neoplasm of adrenal cortex, accelerated essential or renal hypertension, iatrogenic
9 Excessive secretion or administration of glucocorticoids	9 Cushing syndrome due to pituitary or adrenal cortical neoplasm iatrogenic
10 Abnormal catabolism and decreased conjugation of glucocorticosteroid, with more free steroid available	10 Essential hypertension?
11 Arteriosclerosis and narrowing of systemic blood vessel	11 All hypertension eventually
12. Increased work and force of contraction and myocardial hypertrophy	12 All hypertension eventually
13 Increased blood volume and/or cardiac output	13 Acute glomerulonephritis, very early essential hypertension (some cases) hypertension in Graves disease
14 Mechanical obstruction of aorta	14 Coarctation of the aorta
15. Increased blood viscosity	15 Polycythemia (Gaisbock syndrome)?
16. Atherosclerosis of aorta and large blood vessels	16. Systolic hypertension of the aged (rarely pure)
17 Increased stroke output	17 Aortic insufficiency Heart block

secretion of renin by the juxtaglomerular cells.[14] These mineralocorticoids and their metabolites are excreted largely in the urine.[11]

The renin-angiotensin system begins by the secretion of renin from the juxtaglomerular cells of the kidney.[13,15] This secretion is believed to be dependent on pressure (stimulated by decreased stretch) although the evidence for this is still incomplete.[14] The cells are inhibited by aldosterone. Renin reacts with plasma α_2 globulin (angiotensinogen) to produce a decapeptide the relatively inactive angiotensin I which is converted by converting enzyme into the octapeptide, angiotensin II (AT).[16,17] AT is distributed by the blood to all tissues, including blood vessels. It is a potent, direct vasoconstrictor. It also stimulates secretion of mineralocorticoids by the zona glomerulosa of the adrenal cortex,[11,15] and has a direct effect on tubular reabsorption of sodium by the renal tubules.[19] There is an ill-defined relationship between the action of AT and sympathetic neural integrity.[60] It is very rapidly inactivated by tissue and blood enzymes, particularly by the peptidase angiotensinase[61,62] and is excreted in the urine as component amino acids and their metabolites.[62]

The myogenic stretch reaction is not neural and takes place largely in the precapillary sphincters.[61] If these sphincters are stretched by increased pressure they tend to react by constricting.[65] This constriction is counteracted by the production of vasodilating metabolites by tissue cells as a response to ischemia and this entire process is called *autoregulation*.[66,67] These reactions are thought to be particularly important in the kidney but have been demonstrated in many other tissues, including striated muscle.[63]

Several examples of the interaction of these systems might be pertinent. It is known that any vasoconstriction such as produced by chronic infusion of NE[69] or as described under catecholamine metabolism in essential hypertension, can increase sodium concentration in the walls of the blood vessels. This may make the vessels more reactive to vasoactive substances and increase vasoconstriction and hypertension.[70,119] Ingestion of sodium is usually but not consistently found to be increased in

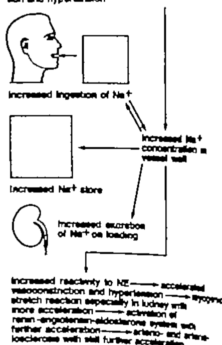


Fig. 4. Metabolism in essential hypertension.

essential hypertension,[71] an... of sodium is increased for a... load (Fig. 4).[72] Recent stud... there is also an increased p... reabsorption of sodium in e... disease.[72] Tracer studies... shown increased stores of... tial hypertension.[73] The... pressure probably influence... the myogenic stretch reac... turn can activate the re... aldosterone system. It h... strated that I[131]-labeled an... appears more slowly from... tients with essential hyper... larly if accelerated than in... probably because of a lar... substance in the hyperte... This occurs despite the... dation of angiotensin II... in the serum of patients... pertension.[62,73] R... levels of lactic... renal hyperte... thought to

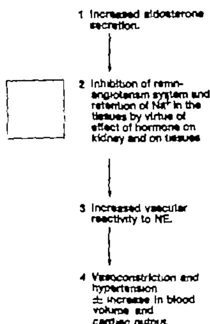


Fig 5 Primary aldosteronism

striction.[75] The hypertensive process progresses further through the development of arteriolosclerosis and arteriosclerosis.

In primary aldosteronism on the other hand sodium is retained in the tissues by virtue of the direct action of the hormone,[76] as well as by its effect on the kidney[77] where it inhibits the excretion of sodium) (Fig 5) This makes the blood vessels more reactive to NE[78] and produces vasoconstriction and hypertension which may be increased further by an increase in blood volume and cardiac output. The renin angiotensin system is inhibited by aldosterone, and the absence of renin in the blood is one of the signs by which primary aldosteronism can be differentiated from the secondary type Why all hyperaldosteronism does not produce hypertension is not understood except that in edematous states the retained sodium may be in the interstitial fluid rather than in the cells and the blood vessels may be resistant to stimulation by vasoactive substances.[79]

The nature of the hypertension produced by the glucocorticosteroids, as in Cushing's syndrome, is unknown These hormones however increase reactivity to norepinephrine in normotensive subjects but not in patients with essential hypertension[80] There is also some evidence of a defect in conjugation as well as other aspects of catabolism of glucocorticosteroids in essential hypertension[81] and less pregnanetriol than normal is found in the urine of these patients.[82]

The action of drugs

The action of drugs used in the treatment of hypertension can only be properly understood in the context of abnormalities in hypertensive mechanisms Thus most drugs presently employed will be found to act either on the catecholamine or electrolyte and hormone mechanism or on the autoregulation complex. In the first category would be reserpine, guanethidine α-methyldopa, and pargyline in the second the thiazide and phthalimidine diuretics and spironolactone and in the third hydralazine and perhaps α-methyldopa which may have a dual effect

The metabolism and action of reserpine, for example, is only imperfectly understood The drug passes through the blood brain barrier easily and depletes both brain and peripheral tissues of NE.[83] It also affects serotonin metabolism in the brain[84] and produces sedation as well as decreased peripheral vasoconstriction and a decrease in heart rate[85] It has little effect on cardiac output or glomerular filtration[86] and decreases standing (chiefly) blood pressure by about 15 or 20 per cent but later supine blood pressure as well It is only effective however in about 20 per cent of the patients Its side actions include production of peptic ulceration and edema (rare) nasal congestion and depressive psychosis.[87]

The metabolism of guanethidine is also incompletely understood but the drug has the virtue of passing the blood brain barrier minimally and therefore of acting chiefly peripherally[88] It depletes NE stores in peripheral sympathetic nerves[89] and produces increased reactivity to infused NE[88,89] but finally a vasodilatation because of inability of the nerves to release NE which is not there. There may be some direct vasodilating action as well but this is not firmly established[91] Glomerular filtration and cardiac output are decreased at first but later become normal[92] The heart rate is decreased[93] Only standing blood pressure is decreased at first but later both standing and supine blood pressures are lowered by

about 25 per cent in about 80 per cent of the patients.[94] Side actions are frequent bowel movements, inhibition of ejaculation postural hypotension with fainting (over dosage) and edema (rare).[98] The drug is best given together with a diuretic.[94]

The action of α-methyldopa (α CH_3D) has been more completely studied. The drug inhibits decarboxylase by competing with dopa.[97] Since this is not a rate-limiting step in catecholamine synthesis, however such synthesis is only partially inhibited by the drug.[99] The drug itself is metabolized by decarboxylase and hydroxylase to α-methyl norepinephrine (α-CH_3NE) which replaces NE in the neural stores.[98] Since α-CH_3NE is relatively nonvasoconstrictive vasoconstriction is decreased and blood pressure is lowered.[8] This drug lowers supine as well as standing blood pressure,[100,101] and probably dilates peripheral arterioles and precapillary sphincters directly in addition to its effect on NE stores. It produces drowsiness at first but later has little effect on the brain because it passes the blood-brain barrier with difficulty.[101] It tends to increase glomerular filtration as well as cardiac output or leaves them unchanged.[102] The heart rate may be slowed but this is an inconsistent effect. Blood pressure is lowered by about 25 per cent in about 60 per cent of the patients, although tolerance may become a problem in management.[103] Side actions are initial drowsiness, skin eruption and hepatotoxicity (rare).[94]

The metabolism and mode of action of pargyline hydrochloride a monamine oxidase inhibitor is also incompletely understood. Theoretically since it inhibits the degradation of NE, it should produce hypertension rather than hypotension. The first step in NE degradation in the peripheral tissues however is O-methylation rather than amine oxidation of NE,[98] so that inhibition of the latter enzyme has no effect on tissue concentration of NE. One theory holds that pargyline inhibits amine oxidation of NE in sympathetic ganglia where monamine oxidase (MAO) is alleged to provide the first step in the degradation of NE.[104] In the ganglia, NE acts to inhibit the acetylcholine-cholinesterase system which is the transmitter of nerve impulses. Hence the accumulation of NE acts like ganglion blockade. A more recent theory holds that pargyline blocks the release of NE at nerve endings.[107] This could be due to the accumulation of tyramine and its metabolite octopamine and other amines, in addition to NE in the sympathetic neural stores. The mixture released by neural discharge would however thus be less potent than NE alone. Pargyline passes through the blood brain barrier and acts as a mood elevator presumably because it inhibits brain MAO and causes the accumulation of serotonin and NE there.[108] In the brain, monamine oxidase rather than O-methyl transferase is believed to provide the first step in the degradation of NE.[109] The drug has little effect on glomerular filtration or cardiac output except to decrease them somewhat, especially at first.[110] It also produces postural hypotension but, as with other drugs, supine blood pressure is also decreased later.[111] It is effective in about 80 per cent of the patients and produces on the average about a 20 per cent decrease in blood pressure.[112,113] Unlike some of the older MAO inhibitors, it is not hepatotoxic.[114] Optic atrophy is a very rare side effect, and postural hypotension with syncope may result from overdosage.[115] MAO is the chief enzyme for degrading tyramine. When liver MAO is inhibited by the drug the ingestion of certain cheeses and wines which contain tyramine may lead to severe hypertensive crises, with cerebral hemorrhage in some cases.[115] The ingestion of such substances must be prohibited in patients who are being treated with pargyline.

The thiazide and phthalimidine diuretics act both in the tissues and on the kidney. In the kidney they inhibit tubular reabsorption and increase excretion of both sodium (Na^+) and potassium (K^+).[116] In the tissues they probably influence the transport and distribution of these ions between intracellular and extracellular spaces.[117] The drug thus depletes intracellular and extracellular stores of Na^+ and K^+. At first blood volume cardiac output and glomerular filtration are decreased in proportion to blood pressure but later these functions return to normal despite a persistent decrease in blood pressure.[118] Vascular reactivity to NE, however remains decreased especially in hypertensive subjects.[1] Both standing and supine blood pressures ar

creased by about 15 per cent by these drugs in about 85 per cent of the patients. However, these drugs increase serum uric acid and may produce attacks of gout.[illegible] They also can increase blood sugar and may precipitate diabetes in susceptible patients.[illegible] Serum K^+ is frequently decreased, and this may cause cardiac arrhythmias, especially if digitalis is given concomitantly.[illegible] In patients with renal insufficiency, these drugs may increase azotemia.[illegible] They also occasionally produce skin rashes and gastrointestinal irritation.[illegible] The potassium chloride incorporated in enteric-coated thiazide-containing capsules may on occasion produce small intestinal ulceration.

Spironolactone acts by competing with aldosterone for the renal and tissue receptor sites which this hormone affects. It is, therefore, an aldosterone inhibitor.[illegible] It increases renal Na^+ excretion, thus, by inhibiting the usual Na^+-conserving effect of normally or excessively secreted aldosterone and other salt retaining hormones.[illegible] For this reason, as well as by virtue of a direct effect on tissues, it depletes intracellular and extracellular tissue stores of Na^+ without depleting K^+.[illegible] In renal insufficiency, however, it may increase serum K^+ concentration.[illegible] It is not known whether this drug, like the thiazides, produces at first a decreased blood volume, cardiac output, and glomerular filtration, which later become normal despite a persistent decrease in blood *pressure*. Whether the decrease in blood pressure is due to a decrease in vascular reactivity to NE has also not been demonstrated as yet. Both supine and standing blood pressures are decreased by about 15 per cent, especially in patients with hypertension.[illegible] The drug is effective in about 85 per cent of the patients. A rare side action is breast stimulation.[illegible] The drug is contraindicated in severe or moderately severe renal insufficiency because of its effect on K^+.

Despite many years of investigation the exact mode of action as well as the metabolism of hydralazine are still incompletely understood. The drug passes the blood-brain barrier, and the belief at one time was that it inhibits sympathetic outflow through the nerve pathways of the brain which eventually release sympathetic nerve NE.[illegible] It is now known, however, that sympathetic outflow is actually increased. There is a direct dilating action of the drug on peripheral blood vessels, including the precapillary sphincters.[illegible] This decreases blood pressure, but because of a consequent decrease in baroreceptor activity, sympathetic outflow is increased and modifies the decrease in blood pressure produced by the direct action of the drug.[illegible] Hydralazine increases cardiac output, heart rate, and glomerular filtration.[illegible] The decrease in blood pressure produced by the maximally permissive dose (300 mg. daily) is small (about 10 per cent) in most patients treated. Side actions are tachycardia, angina pectoris, gastric irritation, and rarely a syndrome similar to systemic lupus erythematosus, especially with overdosage.[illegible]

All these drugs should be used judiciously and in combination where indicated and individualized for each patient. They reduce mortality and morbidity in accelerated hypertension and, most believe, in simple essential hypertension as well. The major contraindication to their use is renal insufficiency, especially when severe.

Summary

1. Various hypertensive mechanisms and the known links between them are described, including abnormalities in catecholamine metabolism and in hormone, electrolyte, and tissue metabolism.

2. Drug therapy is discussed in the frames of reference provided by these abnormalities.

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Fundamentals of clinical cardiology

Left bundle branch block—A clinical assessment Part II*

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Ballistocardiogram

Normal ballistocardiogram (Fig. 15). The genesis of the waves of the normal ballistocardiogram is still controversial. The ballistocardiographic wave form may be subdivided into systolic waves and diastolic waves. The H wave is the first major upward deflection; this is followed, in turn, by a somewhat deeper downward deflection called the I wave.[114]† The second positive wave is of greater amplitude and is known as the J wave, and the second downward or footward deflection is the K wave, which ordinarily is as deep as, if not deeper than, the I wave. These four wave components constitute the systolic portion of the ballistocardiogram. Wave forms of lower amplitude occur in diastole and have been called the L (positive), M (negative), and N (positive) waves.

The genesis of the H wave is still obscure. The beginning of the H wave coincides with the first heart sound, and the tip of the H wave occurs about 0.05 sec. after the beginning of the first heart sound.[111,112] The onset of the H wave is associated with isometric ventricular contraction.[11,11] Right ventricular ejection begins just before the tip of the H wave, whereas left ventricular ejection begins after the tip of the H wave and coincides with a flexure on the HI segment.[112] Thus, the first part of the HI segment corresponds to right ventricular ejection, and the second portion of the HI segment corresponds to left ventricular ejection.[113] Consequently, these workers have associated the H wave with ventricular function.[11]

Nickerson[11] has associated the H wave with atrial systole, whereas DeLalla and associates attribute it to a combination of the apical thrust and atrial contraction. Left ventricular ejection begins about 0.035 sec. after right ventricular ejection, and thus begins between the H and the I flexure.[11,113] As noted by Braunstein,[111] regardless of its cause, the H wave does obscure the early part of the recoil phenomenon. What is left of the footward and downward recoil is known as the I wave.[11]

Reeves[117] believes that the HI downstroke may be an important representation of the acceleratory function of the left ventricle. With the wide frequency range force ballistocardiogram, a small notch (I+) has been recorded near the nadir of the I wave in about one third of normal subjects. Reeves[117] has also repeatedly

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†For list of References, see Par[illegible] the October [illegible]

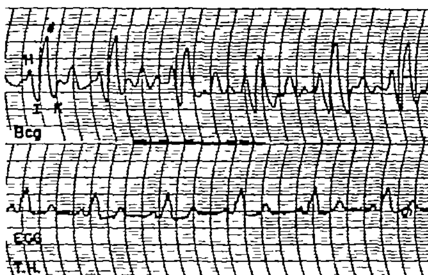


Fig 15 Patient T H The upper tracing (*Bcg*) illustrates a normal ballistocardiogram. The lower tracing (*ECG*) is Lead I of the simultaneously recorded electrocardiogram displaying left bundle branch block. Note that the T waves are upright This patient is a 45-year-old white man with a history of mild coronary insufficiency followed by the appearance of left bundle branch block No hypertension congestive failure, or cardiac enlargement. The patient also has muscular dystrophy of the facioscapulohumeral type

found the H to be exaggerated in various forms of myocardial disease

The J wave is the most conspicuous headward wave in the ballistocardiogram and is thought to be the resultant of abrupt changes in the direction of the blood when the blood is displaced headward from the right ventricle to the pulmonary artery bifurcation and when the headward displacement of the blood reverses its direction around the aortic arch [111] The peak of the J wave has been shown by electrokymography to correspond to the end of the phase of rapid ejection of both ventricles.[114] The phase of rapid ventricular ejection then corresponds to the HJ interval [111]

Following the J wave the footward deflection or K wave is inscribed and has been thought to be related to the abrupt slowing of flow at the end of systole in the lower portion of the aorta and its branches.[111]

The end of left ventricular systole and the onset of the second heart sound coincide and this occurs at about the time of the upstroke of the L wave [111] The MN interval coincides with the rapid filling phase of ventricular diastole and there is a close relationship between the N wave of the ballistocardiogram and the third heart sound [111]

Ballistocardiogram in conditions commonly associated with left bundle branch block

HYPERTENSION AND HYPERTENSIVE HEART DISEASE. In hypertension before the myocardium has been impaired the amplitudes of the I and J waves are diminished This diminution is accompanied by an extremely deep K wave. However the respective nadir and peak of the I and J waves are not late in time When the myocardium becomes impaired in hypertension the late downstroke pattern or the late M pattern usually results[114] (Fig 16)

CORONARY ARTERY DISEASE. When coronary artery disease is present, the early M pattern late M pattern or "late downstroke" pattern may be encountered or if the myocardium is sufficiently impaired the pattern may be highly disordered Accentuation of the height of the H wave ("early M" pattern) rarely occurs, if ever in conditions other than coronary artery disease.[111]

Ballistocardiogram in left bundle branch block In the normal heart the headward ejection of blood from the right ventricle begins just before the peak of the H wave whereas ejection from the left ventricle does not begin until the downstroke of the H wave, and this is marked particularly

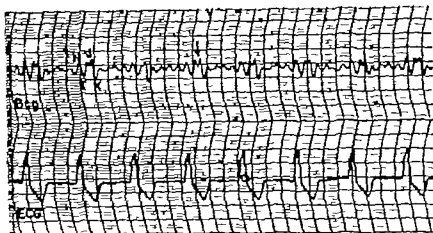


Fig. 16. Patient M. T. The upper tracing (*Bcg*) exhibits a typical "late M" pattern which is present in all phases of respiration. This "late M" is characterized by a double peaked J wave, as indicated by the arrow (*see text*). The lower tracing (*ECG*) is the simultaneously recorded Lead I of the electrocardiogram, showing left bundle branch block. The patient is an 82 year-old Negro woman with arteriosclerotic and hypertensive heart disease, borderline congestive failure, and marked cardiomegaly.

in some of the acceleration ballistocardiograms, with a small flexure on the HI segment.[113] This normal asynchronism between right and left ventricular ejection does not otherwise apparently affect the ballistocardiogram.[113]

In left bundle branch block it has been established that there is a delay in the onset of left ventricular ejection. The "late M" type of ballistocardiogram has been attributed to a lack of synchronism in the contraction of the two ventricles and is characterized by a double J peak.[11] (Fig. 16). It is interesting and rather surprising that this pattern only seldom occurs in left bundle branch block; the explanation offered is that the delay in contraction of the two ventricles in left bundle branch block is usually insufficient to notch the J wave provided that the initial snap of the left ventricle is unimpaired. This "late M" pattern on the other hand has usually been seen when one ventricle ejects its blood in an essentially normal fashion and the other ventricle ejects the major part of its blood late in systole because of myocardial weakness.[11] Braunstein[1] has suggested that a differential in muscle tone between the two ventricles is apparently necessary to produce this pattern.

Nevertheless, the notched J peak or the late M pattern has been described occasionally in left bundle branch block[119, 120] (Fig. 16).

Many patients with left bundle branch block may have normal ballistocardiograms[114-120] (Fig. 15). Mandelbaum and Mandelbaum[19] studied 28 patients with complete left bundle branch block and found that 10 of these patients (35.7 per cent) showed ballistocardiograms which were normal or only slightly abnormal. They found that these essentially normal ballistocardiograms correlated well with the clinical impression that the patient had good myocardial function in spite of the left bundle branch block.

These same workers[119, 120] found that the abnormalities of the ballistocardiogram in patients with left bundle branch block associated with hypertensive or coronary artery disease were similar to those encountered in these latter two conditions without bundle branch block. In other words they usually were associated with a deep JK segment and a low IJ stroke. These workers found moderate or marked abnormalities in the ballistocardiogram in 18 of their 28 subjects with left bundle branch block, and in no case in which heart disease was detected clinically was a normal ballistocardiographic record encountered.[11]

Bellet[14] has commented that characteristically in left bundle branch block the ballistocardiogram exhibits ...

J wave and there may also be a diminution of the IJ stroke and a deepening of the K wave. He referred to the work of Mandelbaum and Mandelbaum[119] and their use of the ballistocardiogram to establish or rule out associated organic heart disease and stated that, if these workers found a normal tracing or simply a notched J wave they would conclude that there was no serious underlying heart disease. However Bellet[94] emphasized that more data would be required to settle this point.

Braunstein[11] and Dock and associates[122] believe that when an abnormal ballistocardiogram is seen in left bundle branch block it probably indicates myocardial disease superimposed on the conduction defect.

Moss[11] studied 10 cases of left bundle branch block with the ultralow frequency ballistocardiograph and found in all cases a prominent positive deflection (I+) during the early systolic phase of the ballistocardiogram. He correlated this I+ deflection with delay in onset of left ventricular ejection and suggested that it may represent the same physiologic event as the notched J wave recorded in the high-frequency displacement ballistocardiogram.[119]

In this same study Moss[124] found 2 cases of left bundle branch block in which the ballistocardiograms were otherwise entirely normal whereas in the other 8 cases of left bundle branch block the records were abnormal which he interpreted as being due to ischemic heart disease.

In a series of patients with left bundle branch block Braunstein and Scott[123] have encountered some tracings showing a rounded I tip and some with an I+ (Fig. 17).

The notching of the HI or IJ segments may be seen in the ultralow frequency tracing of normal subjects and hence is not necessarily indicative of left bundle branch block.[124] With the high frequency table however this notching is not seen in normal subjects. With the high frequency table a notching of the HI limb IJ limb or a blunting of the I nadir is consistent with myocardial dysfunction and as such is suggestive of left bundle branch block with some accompanying myocardial disease.[11] The late M pattern suggests a greater degree of left ventricular dysfunction.[1]

Apexcardiogram

Normal apexcardiogram. The normal apexcardiogram has been well described by Benchimol and Dimond[125-129] by Coul-

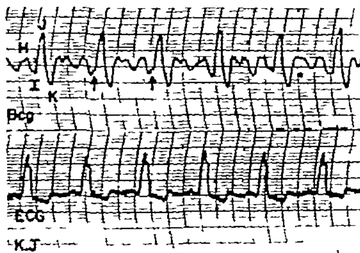


Fig. 17. Patient K. J. The upper tracing (*Bcg*) represents a ballistocardiogram which is essentially normal except for a notch in the lower portion of the I J limb, as illustrated by the arrows. This deformity varies with respiration. It does not occur in the fourth complex. It is seen as a blunting of the nadir of the I tip in the first and last complexes and appears in the lower portions of the H I limb of the fifth complex. The lower tracing (*ECG*) is a simultaneously recorded Lead I of the electrocardiogram showing left bundle branch block. The patient is a 38-year-old Negro woman who has had documented left bundle branch block for 5 years. No cardiovascular symptoms. The patient underwent a total colectomy at age 29 for severe ulcerative colitis.

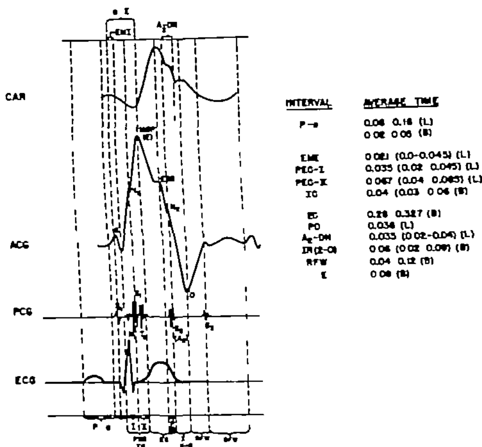


Fig 18 Normal pexcardiogram (adapted from Benchimol and Dimond,[] and Tafur Cohen and Levine[]) *P-a* Interval from onset of P wave in electrocardiogram to onset of a wave in apexcardiogram a wave of pexcardiogram. *EMI* Electromechanical interval. *PEC I* First pre-ejection component *PEC II* Second pre-ejection component *IC* Isometric contraction. *EC* Ejection component. *PD* Protodiastolic phase. *A₂-DN* Interval from aortic closure to dicrotic notch on carotid tracing *IR* Isometric relaxation phase. *2-O* Interval from second sound to O point in pexcardiogram. *RFW* Rapid filling wave. *SFW* Slow filling wave *E* a-to-E interval. *MSP* Maximal systolic peak. *E*. Point of ejection. *ESS* End-systolic-shoulder *O* O point or lowest point on apexcardiogram *N* Notch corresponding to mitral valve closure. *N₂* Notch corresponding to aortic valve closure S_1 First heart sound. *M* Mitral component of first heart sound. *T* Tricuspid component of first heart sound S_2. Second heart sound S_3. Third heart sound. *S* Fourth heart sound *CAR* Carotid pulse tracing *ACG* Apexcardiogram. *PCG* Phonocardiogram. *ECG* Electrocardiogram.

shed and Epstein,[] and by Tafur Cohen and Levine.[] A diagram of the normal apexcardiogram and its relationship to the electrocardiogram carotid pulse and the phonocardiogram is shown in Fig 18

THE A WAVE. The a wave of the apexcardiogram is a reflection of left ventricular filling due to left atrial contraction The peak of the "a" wave coincides with the fourth heart sound[] The "a wave follows the onset of the P wave in the electrocardiogram by from 0 08 to 0 16 sec. and coincides with or shortly precedes by 0 01 to 0 03 sec the onset of the QRS complex in the electrocardiogram[]

ELECTROMECHANICAL INTERVAL (EMI) The interval from the onset of the QRS complex in the electrocardiogram to the onset of the systolic wave of the apex cardiogram averages 0.21 sec and has been termed the electromechanical interval[]

SYSTOLIC WAVE

Pre Ejection Components (Isometric Contraction) During this interval the normal apexcardiogram rises rapidly to a maximal peak Tafur and associates[]

have divided this phase into the first and second pre-ejection components.

(a) First pre-ejection component (PEC I)—The first pre-ejection component extends from the onset of the systolic wave to the onset of the mitral component of the first sound. This was found to average 0.035 sec.; this has also been termed the pre-isometric phase of ventricular contraction. The apexcardiogram has been found to record the earliest portion of left ventricular contraction, and has been found by measurement to begin approximately 0.025 sec. before any rise in left intraventricular pressure. *This is thought to correspond to* the low frequency, low-amplitude vibrations (first component) of the first heart sound and may be due to early contraction of the trabeculae carneae and the papillary muscles.[illegible]

(b) Second pre-ejection component (PEC II)—This interval extends from the onset of closure of the mitral valve to the onset of the upstroke of the carotid pulse or to the maximal systolic peak (MSP) of the apexcardiogram. This interval averages approximately 0.067 sec. The mitral and tricuspid valve closures occur before the maximal systolic peak of the apexcardiogram.[illegible] In splitting of the first sound both major components should precede the peak of the systolic wave.[illegible] Tafur, Cohen and Levine[illegible] have recorded a notch on the ascending limb of the systolic wave in many of their apexcardiograms. This coincides with closure of the mitral valve and has been termed N 1.

Maximal Systolic Peak (E Point). The maximal systolic peak is the highest point reached in the apexcardiogram and corresponds to the E point as described by Benchimol and Dimond.[illegible] This coincides with the onset of the upstroke of the carotid pulse and the beginning of the fourth component of the first heart sound and is a reliable reference point for timing of the opening of the aortic valve and for the onset of left ventricular ejection.

Systolic Wave Ejection Component. The ejection component of the systolic wave extends from the maximal systolic peak, or E point, to the aortic valve closure on the phonocardiogram. This interval ranges from 0.28 to 0.327 sec., depending upon the heart rate.[illegible] Tafur and associates[illegible] have identified this point on many of their apexcardiograms by a distinct notch on the downstroke which they have called N 2.

The systolic wave of the apexcardiogram normally displays a rapid descent from the maximal systolic peak to a plateau at mid-systole. The initial systolic descent of the apexcardiogram shows a reciprocal relationship with the upstroke of the carotid pulse. After the mid-systolic plateau, the systolic wave again shows a secondary rapid descent. It is during this secondary rapid descent that the notch corresponding to aortic valve closure is usually *recorded. The interval from the end* systolic shoulder to the aortic valve closure averages 0.036 sec. in duration and represents the protodiastolic phase.

DIASTOLIC WAVES

Isometric Relaxation. This interval extends from the time of aortic valve closure to the lowest point on the apexcardiogram. A notch on the downstroke of the apexcardiogram may be identified in some records and coincides with the aortic valve closure. The period of isometric relaxation has been found by Tafur and associates[illegible] to average 0.091 sec. This same interval, also termed the "2-O interval," which extends from the aortic valve closure to the O point on the apexcardiogram, has been found by Benchimol and Dimond[illegible] to range from 0.02 to 0.09 sec., with an average of 0.06 sec.

The dicrotic notch in the carotid artery pulse tracing usually shows a lag of some 0.03 sec. after the timing of the aortic valve closure on the phonocardiogram and the N 2 notch when recorded on the apexcardiogram. This lag in the inscription of the dicrotic notch has been attributed to the relatively slow retrograde pulse wave that occurs at the end of ejection.[illegible]

The O point in the apexcardiogram is the lowest point; it marks the onset of the rapid filling wave and corresponds to the opening of the mitral valve. The O point also coincides with the peak of the left atrial "v" wave.

Rapid Filling Wave. The rapid filling wave begins with the O point and rises rapidly to a sharp peak; this peak coincides with the third heart sound in the phonocardiogram. The duration of the rapid filling wave ranges from 0.04 to 0.12 sec.[illegible]

The rapid filling wave also occurs during the "y" descent of the left atrial pressure curve. The peak of the rapid filling wave occurs after the T wave in the electrocardiogram. The amplitude of the rapid filling wave represents 20 to 40 per cent of the height of the total amplitude of the apexcardiogram.[129]

Slow Filling Wave. This wave follows the rapid filling wave and ends at the level of the "a" wave of the apexcardiogram. It represents the slow phase of ventricular filling.

AMPLITUDE. The amplitude of the "a" wave is measured in millimeters of deflection from its base line. The height of the "a" wave is expressed as a percentage ratio of the total amplitude of the apexcardiogram measured from the peak of the systolic wave (E point) to the base line (O point). The normal amplitude of the "a" wave has been found to be less than 20 per cent.[124]

A TO-E INTERVAL. The a-to-E interval is measured from the peak of the "a" wave to the peak of the systolic wave. This has been found normally to average about 0.09 sec.[127]

Apexcardiogram in conditions commonly associated with left bundle branch block

ISCHEMIC HEART DISEASE. In ischemic heart disease the apexcardiogram has been found to display abnormally large "a" waves (greater than 20 per cent of the total amplitude of the apexcardiogram) (Fig. 20). It seems to be well established that the "a" wave of the apexcardiogram represents the reflected ventricular wave during atrial systole.[127] The abnormally large "a" wave frequently found in patients with ischemic heart disease has been thought to indicate an abnormal ventricular filling during atrial contraction. The precise mechanism of this abnormal "a" wave in ischemic heart disease has not been conclusively established but has been thought to be related to the abnormally high ventricular resistance to atrial systole.

a-to-E Interval. The a-to-E interval tends to be prolonged in ischemic heart disease, with an average of 0.13 to 0.14 sec. (Fig. 20).

Systolic wave. Abnormalities in the systolic wave of the apexcardiogram have

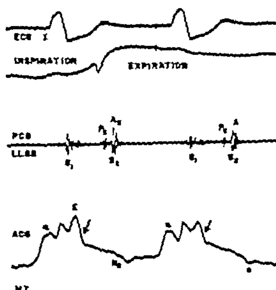


Fig. 19. Apexcardiogram in an 82-year-old Negro woman with left bundle branch block, hypertension, arteriosclerotic heart disease, and congestive failure. No history of myocardial infarction. The "a" wave is very large, with increased duration (0.12 sec.) and increased "a"-wave ratio (> 20 per cent). The a-to-E interval is prolonged (0.18 sec.). The systolic wave has a distinct bifid contour. The arrow indicates the rapid downstroke of the systolic component. *ECG-I*, Electrocardiogram—Lead I. *PCG*, Phonocardiogram. *LLSB*, Left lower sternal border. *ACG*, Apexcardiogram. *a*, "a" wave. *E*, Point of ejection. *N*, Notch corresponding to aortic valve closure. *O*, O point.

been encountered in ischemic heart disease. These changes in the systolic wave occur after the E point and represent an abnormality in cardiac contraction during the period of rapid ejection.[127]

Systolic bulge. A prominent late-systolic bulge occurring at about the time of the second heart sound has been recorded in patients with arteriosclerotic heart disease and myocardial infarction.[127] It should be noted at this point that some normal subjects will display a late-systolic bulge in their apexcardiogram.[135] In the illustration of a late-systolic bulge in a normal subject it was found to occur at end-systole shortly before closure of the aortic valve.[131]

Rapid filling wave. An increase in the amplitude of the rapid filling wave h[illegible] been found in cases of ischemic he[illegible] disease. The prominent rapid filling is commonly associated with a th[illegible] heart sound.

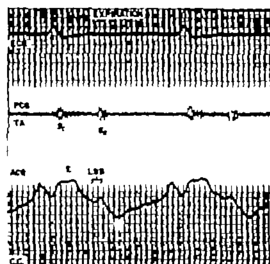


Fig. 20. Apexcardiogram in a 75-year-old Negro man with ischemic heart disease, left bundle branch block, and minimal congestive heart failure. The "a" wave is very large, the "a" wave ratio is increased (> 20 per cent). The a-to-E interval is prolonged. There is a late-systolic bulge (*LSB*). *ECG-I*, Electrocardiogram—Lead I. *PCG*, Phonocardiogram. *TA*, Tricuspid area. *ACG*, Apexcardiogram. *a*, "a" wave. *E*, Point of ejection. *LSB*, Late-systolic bulge. *O*, O point.

SYSTEMIC HYPERTENSION. Patients with arterial hypertension often display a large "a" wave in their apexcardiogram, a sustained systolic wave, and a prolonged a-to-E interval[139] (Fig. 19). These changes are quite similar to those encountered in ischemic heart disease.[72]

The very prominent "a" waves, which are increased in amplitude and often increased in duration, have been described in both ischemic and hypertensive heart disease. These patterns are not specific since similar abnormalities in the "a" waves have been recorded in patients with subaortic stenosis and in those with valvular aortic stenosis.[138] Tafur and associates[138] cite from the work of Braunwald and co-workers[134] that in instances of left ventricular hypertrophy the decreased passive filling of the left ventricle is the result of resistance offered by the ventricle. Atrial systole, therefore, contributes to left ventricular filling, and the prominent "a" waves recorded in the apexcardiogram are a nonspecific effect of left ventricular hypertrophy.

Apexcardiogram in left bundle branch block. At the time of this writing very few apexcardiograms recorded by means of the newer techniques have been published in cases of left bundle branch block.

In 1935, Wolferth and Margolies[14] recorded the apexcardiograms in 5 cases of left bundle branch block. Three of these cases displayed a *bifid outward thrust of* the apexcardiogram in early systole. One case displayed a single large apex thrust; this case is of interest because there was intermittent left bundle branch block and the apex impulse showed delay in onset only in the beats with bundle branch block. This record is also of interest because it has a contour that resembles the apexcardiogram in cases which have more recently been recorded in valvular aortic stenosis. Wolferth and Margolies[14] had one case with a bifid apexcardiogram, the first component of which preceded ventricular systole. Inspection of this record in their article shows that this first wave was, in fact, probably a large "a" wave. These workers observed that a bifid systolic apex impulse was not always recorded in left bundle branch block, and furthermore observed that a systolic bifid apex impulse occurred in some cases without bundle branch block. They concluded that a bifid systolic apex impulse could not be depended on as a sign of bundle branch block.

Lewis[177] studied the apexcardiograms in 14 patients with bundle branch block* and found them to be normal in 8 cases, to have a double systolic impulse in 1, and presystolic or protodiastolic impulse in 5. Levine,[18] reporting that he has begun a study of the apexcardiogram in complete left bundle branch block, anticipates that the double apical impulse found in cases of left bundle branch block will probably be different from the double apical impulse recorded in some cases of systemic hypertension.

Benchimol and Dimond[133] have published an apexcardiogram in a case of complete left bundle branch block in a patient with ischemic heart disease. This record displays a large "a" wave, prolonged a-to-E interval, and a prominent

*It cannot be determined from the text how many had left bundle branch block.

systolic bulge. Benchimol[144] has commented that he cannot be certain that left bundle branch block by itself is responsible for the alterations seen in this record He has further noted that the large a wave, prolonged a to-E interval and prominent systolic bulge are not consistently present in patients with left bundle branch block unless the patient has concomitant ischemic heart disease as evidenced by angina pectoris or old myocardial infarction [144]

The systolic component of the apex cardiogram in left bundle branch block may display a rapid downward deflection (Figs. 19 and 21) Benchimol[144] has found this type of rapid downward deflection in 60 per cent of his cases of left bundle branch block.

A very large a wave with increased duration and increased a" wave ratio is commonly noted in left bundle branch block (Figs. 19 and 20) but, as Benchimol[144] has emphasized may be due to associated ischemic heart disease.

The apexcardiogram in Fig 19 displays a large "a wave with increased duration

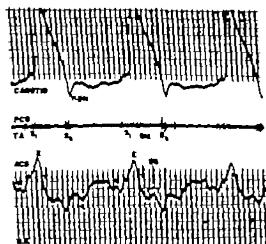


Fig 21 Apexcardiogram in a 65-year-old white man with left bundle branch block. Documented history of paroxysmal atrial fibrillation No history of chest pain or hypertension. The a-to-E interval is prolonged (0.14 sec.) The arrow indicates the rapid downward deflection of the systolic wave A late-systolic bulge is present (SB) *Carotid* Indirect carotid pulse. *DN* Dicrotic notch *PCG* Phonocardiogram. *TA* Tricuspid area *ACG* Apexcardiogram. a a wave. *E*, Point of ejection *SB* Systolic bulge. *O* O point

and increased a wave ratio the a to-E interval is prolonged The systolic wave is abnormal with a bifid contour and a rapid downstroke. This patient has hypertension ischemic heart disease and congestive failure.

The apexcardiogram recorded in Fig 20 shows a very large a wave, an abnormal a wave ratio a prolonged a to-E interval and a late-systolic bulge. The tracing in Fig 21 also shows a late-systolic bulge and a prolonged a to-E interval

Benchimol and Dimond[145] recorded the apexcardiogram in a young woman with left bundle branch block and no other demonstrable heart disease and found the tracing to be normal

Electrocardiogram in left bundle branch block with myocardial infarction

In 1945 Wilson and associates[146] made some very astute observations concerning the electrocardiogram in cases of myocardial infarction complicated by left bundle branch block "In the presence of left bundle branch block it is seldom possible to make a diagnosis of myocardial infarction on the basis of the electrocardiographic findings alone When the ventricular septum is intact the potential of the cavity of the left ventricle is initially positive and this prevents the occurrence of the prominent Q or QS deflection which play such an important role in the electrocardiographic diagnosis of infarction. Characteristic changes *in the level* of the RS-T junction in the form of the RS-T segment and in the shape of the T deflection may occur but they are usually obscured by the alterations of the T complex produced by the conduction defect It is chiefly when the area of QRS happens to be small that distinctive electrocardiographic changes of this sort are encountered

The same authors[146] further observed Infarcts which destroy a large amount of septal muscle may prevent the occurrence of this initial positivity of the left ventricular cavity and lead to the appearance of Q or QS deflections in the leads from parts of the precordium overlying the infarct of the free wall of the left ventricle even though left branch block is

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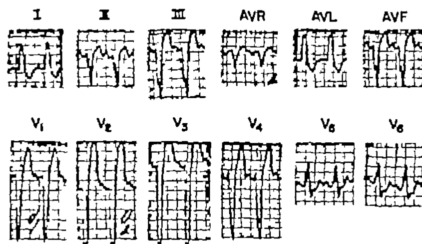


Fig. 23. Patient W. K. Left bundle branch block. QRS duration 0.16 sec. Abnormal left axis deviation of terminal QRS forces (−45 degrees). Notching of the S waves in Leads II, III, and aVF. Deep S waves in the right precordial leads; the true depth of these waves is not evident because they are technically foreshortened. Marked S-T segment elevation in the right precordial leads, reaching 20 mm. in Lead V2. Broad, slurred R waves in Leads V5 and V6 with small S waves. The Lewis index is +38 mm. *Clinical:* A 51-year-old white man with a long-standing history of chronic glomerulonephritis and hypertension. *Autopsy:* The heart was massively hypertrophied. The total heart weight was 920 grams. LV free wall, 464 grams; LV + IVS, 630 grams; RV free wall, 106 grams (Table II, A-64). The increase in muscle mass was most prominent in the left ventricle, which was also slightly dilated. There was moderate coronary atherosclerosis, with luminal narrowing rarely exceeding 30 per cent. There was no evidence of old or recent myocardial infarction.

left bundle branch block is suggestive of interoseptal ischemia, whereas T-wave inversion in Leads II, III, and AVF in left bundle branch block is suggestive of ischemia of the inferior wall.[44]

Old myocardial infarction

INFARCTION OF THE FREE WALL OF THE LEFT VENTRICLE (FIG. 24,A). In left bundle branch block the left intraventricular cavity is initially positive, displaying a large R wave. As was emphasized by Wilson and co-workers,[49] an electrode overlying a necrotic zone in the free wall of the left ventricle will likewise display an initial positivity or an R wave and will not permit the diagnosis of left ventricular infarction. Sodi-Pallares is in accord with this concept and states, "If the interventricular septum itself is not involved in the necrosis of infarction, that is, if the free wall is the only part affected, it is impossible in the majority of cases to make a diagnosis of myocardial infarction."[44]

In some cases of infarction of the lateral left ventricular wall an RS pattern is recorded in Leads V5, V6, and Lead I. The S wave has been explained as a reflection of the cavity potential which is an RS pattern. Massie and Walsh[41] have explained the S wave as being due to the failure of the infarcted portion of the free left ventricular wall to generate potential during the terminal portion of the QRS interval, thus allowing forces directed away from the effective electrical site of the infarct to become preponderant. Caution must be exercised in employing this RS pattern in the left precordial leads as indicative of infarction, since it may occur in uncomplicated left bundle branch block.[3] This RS pattern in the left precordial leads in uncomplicated left bundle branch block may be related to displacement of the transition zone to the left[13, 41, 44] (Fig. 23). Of help is the T-wave configuration. Often in transitional RS patterns in the precordial leads the T waves are upright, whereas if the T waves are strongly inverted or of the coronary type, the diagnosis of infarction is more likely.[44] As emphasized by Massie and Walsh,[41] terminal S waves in Lead V6 in uncomplicated left bundle branch block may be related to the downward tilt of the V6

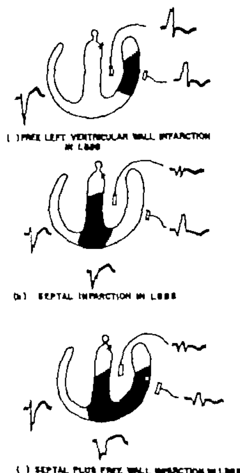


Fig 24 Diagram of the electrocardiographic patterns obtained in left bundle branch block with myocardial infarction (adapted from Sodi-Pallares et al[illegible]) The shaded zones indicate myocardial necrosis.

lead axis, causing the terminal portion of the frontal QRS loop to project on the negative half of the V₆ lead axis. These same authors also emphasized that terminal S waves in Leads I and V₆ in otherwise typical left bundle branch block are of questionable diagnostic value unless a serial change is observed in the electrocardiogram with the appearance of S waves in leads which previously had displayed no S waves (again presumably without any displacement of the transition zone) or with accompanying S-T segment or T wave changes suggestive of acute infarction

INFARCTION OF THE INTERVENTRICULAR SEPTUM (FIG 24 b) Sodi Pallares and associates[illegible] have especially emphasized that when infarction involves the interventricular septum in left bundle branch block, pathognomonic alterations in the QRS complex are often readily detected A lead from within the left ventricular cavity in the presence of left bundle branch block complicated by massive septal infarction is initiated by a large Q wave (QR or Qr pattern) This Q wave is thought to reflect the early negativity of the right ventricular cavity and is detected in the left ventricular cavity because the necrotic septum acts only as conductive tissue[illegible] This Q wave may also be recorded in the left precordial leads and in Lead I Sodi Pallares believes there is a direct relationship between the depth and duration of this Q wave and the extent of septal involvement and thus a measure of the upward extension of the infarct in the septum He has distinguished between infarction of the inferior one third of the septum and the so-called massive infarction of the septum which involves the inferior half or two thirds with only the basal segments being spared In massive infarction of the septum complexes of the notched QS type are encountered in the mid-precordial leads. Sodi Pallares attributes these patterns (qrs, QrS) to the fact that the electrodes are oriented to the high intact portion of the interventricular septum and believes that the height of the R wave is proportional to the amount of tissue spared in the interventricular septum If the amount of tissue spared is small the mid-precordial leads may show a QS pattern which is notched When the infarction is confined to the lower third of the septum the R waves are taller in the mid and left precordial leads, which suggests less septal involvement

With extensive septal infarction the initial right to-left septal depolarization is often eliminated permitting electrical forces in the free wall of the right ventricle to become dominant[illegible] The R waves which may occur in the right precordial leads in cases of left bundle branch block with septal infarction have been attributed to this activation of the free right ventricular wall with the early QRS vectors oriented to the right and anteriorly With

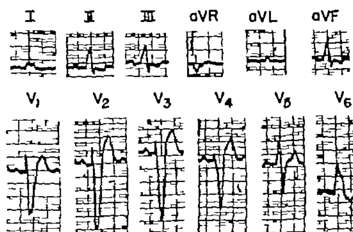


Fig. 25. Patient I. H. Oct. 28, 1960. Left bundle branch block. QRS duration 0.15 sec. Small but distinct Q waves in Leads I, aVL, and V[illegible]. Low secondary peak of the R wave in Lead V[illegible]. R waves in Leads V[illegible] and V[illegible] relatively tall, measuring 6 mm. and becoming progressively smaller in Leads V[illegible] and V[illegible]. *Clinical:* A 48-year-old Negro man with a history of cardiac enlargement for 18 years, labile hypertension and congestive failure for 6 years. *Autopsy:* The heart was enlarged, weighing 890 grams. Both the right and left ventricles were hypertrophied and dilated. There was moderate focal fibrosis but no evidence of old or recent myocardial infarction. The coronary arteries were patent throughout; there was mild coronary atherosclerosis.

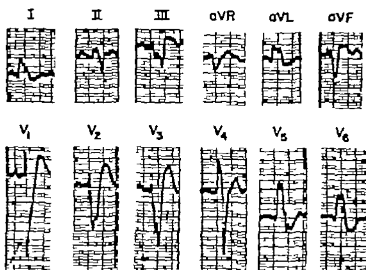


Fig. 26. Patient C. M. Sept. 11, 1961. Left bundle branch block. QRS duration 0.16 sec. Abnormal left axis deviation of terminal forces (−45 degrees). Small but definite Q waves present in Leads I, aVL, V[illegible], and V[illegible]. S-T segment elevation with terminal T wave inversion in Lead III. Distinct notching on the downstroke of the S wave in Lead V[illegible]. Abnormal R-wave progression in the precordial leads, with the R wave unusually tall in Lead V[illegible], measuring 7.5 mm., and becoming progressively smaller in Leads V[illegible] and V[illegible]. *Clinical:* A 87-year-old Negro man with a clinical history of hypertensive and arteriosclerotic heart disease with coronary insufficiency. *Autopsy:* The heart weighed 735 grams; there was marked left ventricular hypertrophy. The coronary arteries displayed a severe degree of atherosclerosis but no occlusion. There was patchy subendocardial fibrosis but no evidence of old or recent myocardial infarction.

massive septal infarction there may be progressive diminution in the height of the R wave from Lead V_1 to Lead V_4. This so-called reversal of the R wave progression in the precordial leads has been well demonstrated in proved cases of septal infarction in left bundle branch block. On the other hand this same pattern may occur in uncomplicated left bundle branch block[13,18] and should not by itself be used to absolutely diagnose septal infarction (Figs. 25 and 26).

INFARCTION OF THE SEPTUM PLUS THE FREE LEFT VENTRICULAR WALL (FIGS. 24 C AND 27). When there is massive infarction of the interventricular septum the electrocardiographic findings noted above are again encountered: (1) Q waves in Leads V_5, V_6, and I (aVL). (2) Notched QS or qrS (QrS) pattern in the precordial Leads V_1-V_4 (V_5). (3) Progressive diminution of the R wave from Lead V_1 to Lead V_4.

The left ventricular cavity lead shows a Qr pattern because of the septal infarction. The electrodes overlying the infarcted zone of the lateral free wall show a pattern similar to that from within the cavity of the left ventricle (QrS or qrs). The r wave is small because, in massive infarction of the septum, only a small zone of the superior portion of the septum is usually spared. The S wave is thought to be the result mainly of the late septal forces being oriented superiorly and also of outwardly directed forces in the uninvolved portion of the free left ventricular wall. Sodi-Pallares has further suggested that if the high lateral portion of the free left ventricular wall is involved by necrosis, S waves may also be encountered in Leads I and aVL.

If the septal infarction is less extensive, the Q waves encountered in Leads V_5, V_6, aVL, and I are of less magnitude and duration than in massive infarction and the R waves in these same leads are taller when there is less extensive septal involvement.

Autopsy and electrocardiographic correlation studies in left bundle branch block

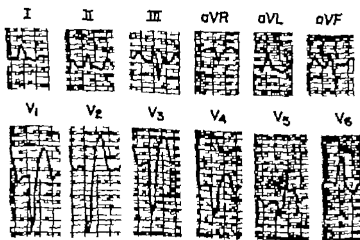


Fig. 27. Patient C. Cr., April 2, 1958. Left bundle branch block. QRS duration 0.17 sec. Q waves in Leads aVL (0.03 sec.), I (0.02 sec.), and V (0.02 sec.). Embryonic r wave in Lead V. QR pattern in Lead V_6, with S-T segment elevation and T inversion. This tracing is indicative of an anteroseptal myocardial infarction in the presence of left bundle branch block. The S-T segment elevation suggests that the infarct is either acute or subacute. Clinical: A 52-year-old white man who was hospitalized as an emergency case because of the sudden onset of severe crushing chest pain that radiated to his neck and arm. There was a past history of a heart attack in 1944 with 8 weeks of hospitalization. A history of hypertension. The patient died suddenly 2 days after admission, April 4, 1958. *Autopsy*: The heart weighed 705 grams. The left ventricle was hypertrophied, measuring 18 mm. in thickness. There was a moderately severe degree of sclerosis of the coronary arteries, but no complete occlusion was found. A large ventricular aneurysm, about 6 cm. in diameter involved the anterior and inferior portions of the left ventricle, adjacent septum and apex. The wall of the aneurysm was calcified and measured only 2 mm. in thickness. No histologic evidence of recent infarction could be detected in the sections reviewed.

complicated by myocardial infarction. Several authors[18,146,147] have attempted to correlate various electrocardiographic criteria for the diagnosis of myocardial infarction complicated by left bundle branch block with autopsy studies. Chapman and Pearce[19] and Rhoads and co-workers[147] evaluated only cases with autopsy-proved infarction and had no control cases of left bundle branch block without infarction. Besoaín-Santander and Gómez Ebensperguer[146] had 6 autopsy-proved cases with infarction and 20 without infarction.

Norris and Scott[4] have studied a battery of proposed electrocardiographic criteria for the diagnosis of myocardial infarction in the presence of left bundle branch block in 85 autopsy-controlled cases. At autopsy 50 patients exhibited no infarction and 35 had myocardial infarction. In the latter group infarction was limited to the left ventricular free wall in 14 cases and involved the interventricular septum alone or the interventricular septum and the left ventricular free wall in 21 cases. A list of the electrocardiographic criteria evaluated in this study is given in Table IV together with the incidence of occurrence in the Control and Infarction groups. It is readily apparent that many

Table IV. Diagnostic value of electrocardiographic criteria for the detection of myocardial infarction in the presence of left bundle branch block

		Infarction group (35 cases)	
Criteria	Control group (50 cases)	Septal or Septal + LV free wall (21 cases)	LV free wall only (14 cases)
	(%)	(%)	(%)
1. Q waves in Lead aVL	52	43	36
Lead I	24	24	14
Lead V_5	6	5	14
Lead V_6	4	5	7
2. QS pattern in Leads V_5, V_6	None	None	None
3. Early (0.03 sec.) notching of S waves in Leads V_3, V_4	8	29	14
4. Late (0.05 sec.) notching of S waves in Lead V_3, V_4	8	24	21
5. rsR pattern in Leads aVL, I, V_5, V_6	16	10	14
6. Abnormal R wave progression in right precordial leads	28	43	21
7. Abnormal R wave progression in right precordial leads plus Q waves in left precordial lead	4	7	None
8. Deep S waves in Lead V_6 with normal transition zone	10	10	7
9. Low primary peaks in R wave in Lead V_5	6	None	None
10. Low secondary peak in R wave in Lead V_5	8	None	None
11. Notched R or R waves in Lead aVF or III	26	33	14
12. "W" complexes in Lead II	4	14	7
13. Initial early notching of S wave in Lead aVF	14	17	14
14. Broad RS pattern in at least two left precordial leads, Lead V_4–V_6	None	None	None
15. S-T segment displacement toward major area of QRS complex	None	None	None
16. S-T segment elevation in Lead V_1 or Lead V_2 > 8 mm. or > ½ T wave in absence of digitalis	2	10	7
17. Negative T waves in right precordial leads	2	19	None
18. Peri-infarction block pattern	18	24	7

MI = myocardial infarction.
LV = Left ventricular.

of the proposed electrocardiographic criteria do not serve to identify correctly myocardial infarction.

The incidence of occurrence of Q waves in Leads aVL, I, V5, and V6 in this study should be noted (Table IV). In uncomplicated left bundle branch block, Q waves were quite common in Lead aVL and occasionally were found to be as wide as 0.06 sec. in duration. Q waves occurred in Lead I (although less frequently than in Lead aVL) in uncomplicated left bundle branch block but in no instance exceeded 0.03 sec. in duration. The presence of Q waves in Lead V6 in left bundle branch block without infarction is rare, and in no case did these exceed 0.03 sec. On the basis of this study it was concluded that the occurrence of Q waves of 0.04 sec. or greater in Leads I, V5, or V6 in left bundle branch block should be regarded as being highly suggestive of complicating myocardial infarction.

Notching of the S waves in the precordial leads to the right of the transition zone has been emphasized as an important sign in cases of myocardial infarction complicating left bundle branch block. Chapman and Pearce[10] have directed attention to the occurrence of early notching of the S waves on the downstroke approximately 0.03 sec. after the onset of inscription. Cabrera and Friedland[1,2] have emphasized late notching of the S waves on the upstroke being of at least 0.05 sec. duration. In the study of Norris and Scott,[34] such pronounced notching of the S waves in Leads V3 and V4 was found to be highly suggestive of myocardial infarction in the presence of left bundle branch block, although some cases of notching were also encountered in the Control group.

The electrocardiograms shown in Figs. 22 and 27 are from autopsy-proved cases of myocardial infarction. The tracings shown in Figs. 23, 25, 26, and 28 illustrate some of the pseudoinfarction patterns.

Vectorcardiogram in left bundle branch block with myocardial infarction

Left bundle branch block with septal infarction

HORIZONTAL PLANE

Initial Forces. The initial forces in the horizontal plane in the vectorcardiogram in left bundle branch block with septal infarction are directed anteriorly and

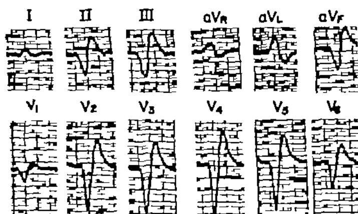


Fig. 25. Patient F. G., March 7, 1964. Left bundle branch block. QRS duration 0.16 sec. QS deflections in Leads V1-V6, with the suggestion of an embryonic [illegible] wave in Lead V5. QS deflection in Lead III; rS pattern in Leads II and aVF. Abnormal left axis deviation of mean QRS (−75 degrees). The QRS forces are directed superiorly and posteriorly. The QS pattern in the precordial leads raises the possibility of an extensive anterior myocardial infarction. *Clinical:* A 73-year-old white man with a clinical diagnosis of chronic obstructive emphysema and arteriosclerotic heart disease with congestive failure. *Autopsy:* The heart exhibited severe hypertrophy and dilatation of all chambers, but this was most prominent in the left ventricle (Table II, A-66). The total heart weight was 850 grams. LV free wall, 350 grams. LV + IVS, 461 grams. RV free wall, 146 grams. There was a mild degree of aortic stenosis (rheumatic). Coronary atherosclerosis resulted in a maximum of 40 per cent compromise of the lumen. There was no recent or old myocardial infarction.

rightward (Fig. 10,7,8). Massie and Walsh[11] have found that the maximal rightward mean instantaneous vector in the horizontal plane lies between +95 and +145 degrees. These same workers found that in uncomplicated left bundle branch block when an anteriorly directed initial deflection was present the maximal instantaneous vector was never to the right of +95 degrees (Fig. 10,4). The duration of this initial rightward portion of the loop in cases of septal infarction was found to range from 0.02 to over 0.03 sec., whereas in those cases of uncomplicated left bundle branch block with a rightward initial deflection the total duration of this part of the loop ordinarily did not exceed 0.015 sec. (Fig. 10,4,7,8).

Cabrera and associates[149] found that in cases of left bundle branch block the best sign of myocardial infarction in the vectorcardiogram was anterior enlargement of the Q loop. In the majority of their cases the initial forces were increased anteriorly and were displaced somewhat rightwardly in the horizontal plane. In some cases the initial forces were decreased and displaced somewhat to the left (Fig. 10,9).

Medrano and associates,[144] studying the vectorcardiogram in dogs with left bundle branch block and septal infarction, found that, when there was infarction of the lower third of the left septal mass, the Q loop increased in voltage, became narrower and pointed more forwardly and sometimes to the right (Fig. 10,7). These workers stated that when the left septal mass was infarcted the electrical forces produced in the lower right septal mass shifted more forwardly and somewhat to the right, giving rise to this characteristic initial loop in the horizontal plane. When there was infarction of both the left and right septal masses, these workers found that the voltage of the Q loop (initial force) in the horizontal plane and the R wave voltage in the right precordial leads were decreased (Fig. 10,9). Infarction of the right lower septal mass was found to result in a decrease or disappearance of the Q loop in the horizontal plane, with the initial forces directed to the right and posteriorly (Fig. 10,10).

Direction of Rotation of the Initial Forces in the Horizontal Plane. In uncomplicated left bundle branch block the initial portion of the loop is usually inscribed in a counterclockwise direction (Figs. 7,8,9 and 10,3,4). In cases of septal infarction complicating left bundle branch block this initial portion of the loop in the horizontal plane shows clockwise rotation in most instances[11,144] (Fig. 10,7). Medrano and associates[144] have observed that the increased voltage of the Q loop and its direction to the right with clockwise rotation are explained by the activation forces of the right septal mass which become prominent because of the disappearance of the electrical forces produced in the infarcted left septal mass.

This increase in magnitude of the initial forces anteriorly and rightwardly in the horizontal plane accounts for the inscription of the Q waves in the left precordial electrocardiographic Leads V_5 and V_6, as well as in Leads aVL and I. This also accounts for an increase in the amplitude of the R wave in Lead V_1, which is then taller than the R waves in Leads V_2 through V_4 (Fig. 29).

Not all cases of left bundle branch block with infarction show clockwise inscription of the initial portion of the loop in the horizontal plane, since some cases may continue to show the initial counterclockwise rotation of the early portion of the loop[149] (Fig. 10,8,9).

QRS Loop. The major portion of the QRS loop in cases of bundle branch block with septal infarction is inscribed in a clockwise direction (Fig. 29). Medrano and associates[144] have observed that the efferent or centrifugal limb points more to the back than it does in cases of uncomplicated left bundle branch block. They have also observed that there tends to be some displacement of this efferent limb of the QRS loop slightly to the right (Fig. 29). These same workers have observed a frequent and valuable diagnostic sign in electrocardiographic leads exploring the free right ventricular wall and right septal mass, namely, slurring lasting 40 milliseconds or more inscribed on the ascending branch of the S wave. This would seem to correspond with the late notching of the S wave described earlier by Cabrera and Friedland.[111]

In septal infarction with left bundle

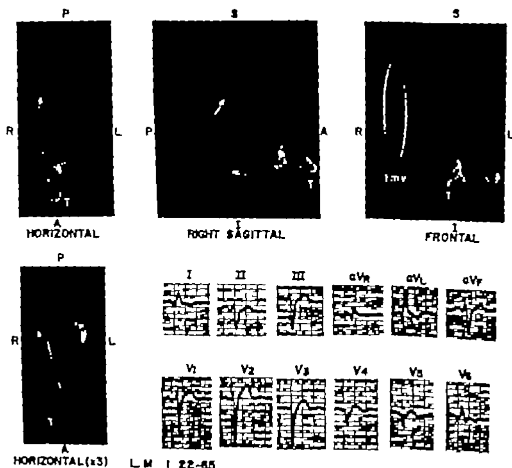


Fig. 29. Patient L. M. Jan. 22, 1965. Left bundle branch block with myocardial infarction. *Vectorcardiogram*. Horizontal Plane—The initial QRS vectors are directed anteriorly and slightly to the right. The QRS loop is inscribed clockwise; the main body of the loop is oriented posteriorly and to the left; the mid and terminal portions are slowly inscribed. The T loop is directed anteriorly. Right Sagittal Plane—The initial vectors are directed anteriorly and inferiorly. The QRS loop is inscribed clockwise; the major portion of the loop is oriented posteriorly and superiorly; the mid and terminal portions are slowly inscribed. The T loop is directed anteriorly. Frontal Plane—The initial vectors are directed to the right and inferiorly. The QRS loop is inscribed counterclockwise and is oriented superiorly; the mid and terminal portions are slowly inscribed. The T loop is directed inferiorly and to the right. *SUMMARY*: The orientation of the initial vectors anteriorly and to the right instead of to the left is consistent with an anteroseptal myocardial infarction. The initial rightward force in the vectorcardiogram correlates with the Q waves in Leads I and V_6 of the electrocardiogram. *Electrocardiogram*: Left bundle branch block. QRS duration 0.13 sec. Q waves in Leads I, aVL, and V_6. QS pattern in Leads V_1-V_4. S-T elevation with upward convexity and terminal T inversion in Leads V_4, V_5. S wave present in Lead V_6. The mean QRS axis is −60 degrees. The initial 0.04 sec. forces are at +60 degrees and the terminal 0.04 QRS forces are at −75 degrees, giving an angle of 135 degrees between the initial and terminal forces. This satisfies Grant's criteria for anterolateral peri-infarction block. The vectorcardiographic pattern is characteristic, however, of left bundle branch block (with anteroseptal infarction), displaying mid and terminal slowing of the QRS loop.

branch block, the R waves are often relatively tall in Lead V_1, diminishing in amplitude in Leads V_2 through V_4. This has been explained by the initial forces being directed to the right and anteriorly, whereas later forces develop in a clockwise direction to the left and posteriorly in the horizontal plane away from the other precordial leads.[44]

Neuman and associates[20] have recently reported similar vectorcardiographic observations in cases of left bundle branch block with myocardial infarction, specifically, enlargement of the initial anterior

forces to the right and anteriorly so that the 0.0275 sec. vector is anterior to the E point (Fig. 10.7,8).

FRONTAL PLANE. Massie and Walsh[11] found that in cases of septal infarction with left bundle branch block the maximal rightward mean instantaneous vector of the frontal QRS loop ranged between +130 and −175 degrees, whereas in most of their cases of uncomplicated left bundle branch block it was impossible to identify a rightward initial deflection in the frontal plane.

In the frontal plane the QRS loop in cases of septal infarction with left bundle branch block may rotate in a counterclockwise or figure-of-eight direction.[11]

Left bundle branch block with infarction of the free left ventricular wall. When there is infarction of the free wall of the left ventricle, the late instantaneous vectors are displaced away from the site of the infarction.[11] These forces which occur late in ventricular activation are deviated posteriorly and rightwardly. In the horizontal plane the QRS loop tends to be inscribed in a counterclockwise direction initially to the left, then posteriorly and leftward, and finally to the right and posteriorly. This late rightward and posterior direction of the QRS loop in the horizontal plane results in the production of S waves in Lead V₆ and Lead I.[11]

The frontal plane QRS loop is inscribed in a clockwise direction to the left, inferiorly, and then to the right.[11]

Neuman and associates[181] described a vectorcardiographic pattern similar to that described by Massie and Walsh[11] in anterolateral myocardial infarction with left bundle branch block, that of displacement of the afferent limb of the QRS loop to the right so that the loop in the horizontal plane rotates in a counterclockwise direction.

Other vectorcardiographic observations in left bundle branch block with myocardial infarction. DePasquale and Burch[182] studied the spatial vectorcardiogram in 15 patients with left bundle branch block and myocardial infarction and noted that with extensive anterior wall infarction there was displacement of the initial portion of the loop away from the infarction with most of the QRSsÊ loop displaced posteriorly. They found one feature common to all of their cases regardless of the site of the infarction, and that was marked distortion of the QRSsÊ loop. They presented a schematic representation of how an infarction in the free wall of the left ventricle with loss of muscle and in turn electrical forces might produce distortions of the QRSsÊ loop.

Burch and DePasquale[77] further noted marked posterior displacement of the QRSsÊ loops in cases of anterior myocardial infarction with left bundle branch block. They observed this to be uncommon in left bundle branch block, except with complicating anterior infarction. The vectorcardiogram in a patient with left bundle branch block and apical and posterior myocardial infarction displayed marked distortion of the QRS loop with superior orientation of the early portion of the loop.

The TsÊ loop is directed opposite to the QRSsÊ loop usually anteriorly, rightwardly, and somewhat inferiorly.[11,182]

Cabrera and associates[183] proposed another vectorcardiographic criterion for the diagnosis of myocardial infarction in the presence of left bundle branch block. This consisted of an intermediate slurring of 10 milliseconds or more superimposed on the clockwise loop of the horizontal plane with the vectors being oriented backward and to the left. These workers did not indicate the precise anatomic location of the infarction.

Vectorcardiographic differentiation of uncomplicated left bundle branch block from anterolateral infarction. In anterolateral myocardial infarction without left bundle branch block the initial forces in the horizontal plane are directed in a clockwise rotation. The 0.01 sec. vector is directed rightwardly and the 0.02 sec. vector is directed posteriorly[183] (Fig. 10.2). In uncomplicated left bundle branch block, as has already been noted, there is clockwise rotation of the QRS loop in the horizontal plane, but the initial portion of the loop ordinarily shows a definite anterior counterclockwise segment lasting from 0.01 to 0.012 sec.[183] (Fig. 10,3). In addition, in left bundle branch block, there is evidence of conduction delay which is not observed in uncomplicated anterolateral infarction.

As noted earlier in a small proportion of patients with uncomplicated left bundle branch block the initial forces may not be directed anteriorly. It is in these cases that the diagnosis of anterolateral infarction may be considered.[84] Again in anterolateral infarction without left bundle branch block there is no slowing of the loop in contrast to the typical slowing in left bundle branch block.

Peri-infarction block

Electrocardiographic criteria. On occasion left bundle branch block may be difficult to distinguish electrocardiographically from anterolateral peri-infarction block with QRS prolongation. The term "peri-infarction block" introduced by First, Bayley and Bedford[86] has been popularized by Grant.[87] The specific criteria proposed by Grant[87] for the diagnosis of anterolateral peri infarction block are as follows: (1) The initial 0.04 sec. QRS vector is directed inferiorly or rightward away from the anterolateral infarct, producing Q waves in Leads aVL and I and broad R waves in Lead III. (2) The terminal 0.04 sec. QRS force is directed markedly leftward toward the anterolateral infarct, resulting in abnormal left axis deviation. (3) The angle between the initial and terminal 0.04 sec. forces is 110 degrees or greater. (4) The QRS may show little or no prolongation or may be prolonged.

In his earlier publications, Grant[3,87] stated that anterolateral peri-infarction block with QRS prolongation could be distinguished from left bundle branch block by the angle between the initial and terminal 0.04 sec. forces. He stated that in left bundle branch block the angle was usually less than 45 degrees, whereas in peri infarction block with QRS prolongation the angle was usually 100 to 110 degrees or greater. Abnormal left axis deviation, he thought also, was less common in left bundle branch block than in peri-infarction block. More recently, Grant has modified his position and has stated that the criteria for the diagnosis of peri-infarction block are less secure in the presence of QRS prolongation.[14]

We have applied Grant's criteria for anterolateral peri-infarction block in the presence of QRS prolongation and have observed some interesting autopsy correlations. When the pattern of anterolateral peri-infarction block was encountered in the electrocardiogram in our cases, we found only about a 50 per cent incidence of actual anterolateral myocardial infarctions. Fibrosis of the interventricular septum or of the free left ventricular wall was frequently encountered in the absence of infarction. Anatomic left ventricular hypertrophy was almost always present.

The electrocardiographic differentiation between anterolateral peri infarction block with QRS prolongation and complete left bundle branch block with infarction may at times be extremely difficult. Further careful anatomic correlations, particularly those in which detailed histologic studies of the conduction system are performed, may be necessary to unravel this problem.[117] In some of our own cases in which the pattern of anterolateral peri infarction block occurred, there was no infarction of the anterolateral wall, but frequent involvement of the anterior portion of the interventricular septum. This raises the intriguing possibility that the anterior or superior division of the left bundle may have been damaged near its site of origin in the septum rather than more peripherally in the free left ventricular wall.

Vectorcardiographic criteria. There have been comparatively few reports dealing with the vectorcardiographic criteria for the diagnosis of anterolateral peri-infarction block.[8,118] Anterolateral peri-infarction block with QRS prolongation and complete left bundle branch block have certain similarities of pattern. (1) In both the time of inscription of the QRS loop is prolonged (0.12 sec. or greater). (2) In the horizontal plane, there is clockwise rotation of the entire QRS loop in anterolateral peri-infarction block, and clockwise rotation of the major portion of the QRS loop in left bundle branch block.

Anterolateral peri infarction block with QRS prolongation and uncomplicated left bundle branch block display certain differential features in the vectorcardiogram. The initial forces in the horizontal plane in anterolateral peri infarction block are displaced to the right and then posteriorly, whereas in uncomplicated left

branch block the initial forces are most commonly directed *anteriorly* and left ward (Fig 10,2,3) In anterolateral peri infarction block the terminal forces are approximately opposite to the direction of the initial forces (180 degrees removed) and tend to be located leftward and su periorly There is terminal slowing (lasting 30 or 40 msec) of the returning limb of the QRS loop in anterolateral peri infarction block whereas in left bundle branch block the slowing begins earlier in the mid portion of the QRS loop

The vectorcardiographic distinction be tween anterolateral peri infarction block with QRS prolongation and complete left bundle branch block complicated by septal infarction is often considerably more dif ficult. In both instances the initial forces are abnormal and may have a similar orientation The later onset of the slowing of inscription in peri infarction block may in some instances permit the distinction from left bundle branch block with septal infarction

More work needs to be done in this field particularly in correlating the vectorcar diographic changes with detailed anatomic studies, including study of multiple histo logic sections of the left ventricular con duction system both in the septum and more peripherally

Permission to record the electrocardiogram and vectorcardiogram on *Patient L.M* (Fig 29) was kindly given by Dr Arnold Iglauer

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Antiarrhythmic drugs. Part VII. Lidocaine as an antiarrhythmic agent

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Lidocaine (2-diethylamino-2, 6-acetoxylidide) is a synthetic local anesthetic which recently has been found to be of value in the treatment of cardiac arrhythmias. During the early years of its use lidocaine was shown to be highly stable, nonirritating locally, with potent analgesic qualities of somewhat longer duration than those of procaine. Lidocaine's action is a rapid one, due to rapid diffusion to, and penetration of, cell membranes.

The drug is cleared rapidly from the blood stream; 20 minutes after intravenous administration none of its effects persist. It is metabolized by hepatic amide-splitting enzymes to release free and conjugated phenols which are found in the urine. Less than 10 per cent is excreted unaltered by the kidney.

The mechanism of the antiarrhythmic effect appears to be similar to that of procaine. Ventricular excitability is depressed with increasing doses, conduction time is slowed and the refractory period is prolonged. Cardiac contractility is not diminished in therapeutic dosages, as may happen with quinidine. In contrast to procaine and procaine amide, doses of lidocaine which produce comparable increases in the diastolic stimulation threshold cause no fall in blood pressure or decreased myocardial contractility.

In 1950 the first cardiac arrhythmia treated successfully with intravenous lidocaine was reported: ventricular fibrillation which occurred during the course of cardiac catheterization of a patient was successfully reverted to regular sinus rhythm with electric shock and lidocaine.

A number of studies in the anesthesiology literature have demonstrated the effects, safety, and dosage ranges when lidocaine is used by continuous intravenous drip. Complete relief of pain occurred at relatively safe levels in patients with intractable pain. When used in conjunction with succinyldicholine (a curare-like drug) for surgical anesthesia (in about 2,000 patients) no significant reactions occurred. When dosage levels above 750 mg. per hour were used, convulsive seizures, controllable with barbiturates, occurred in 3 cases. The intravenous effects of lidocaine were primarily analgesia and drowsiness at the lower dosage levels; with higher doses, anesthesia could be obtained, but this amount approached the convulsive dosage. These and other clinical studies demonstrated that the usual effect of intravenous lidocaine was a slight rise in blood pressure and pulse; occasional decreases were transient in the dosage range utilized. Unanesthetized patients may experience a variety of symptoms from the intravenous administration of lidocaine. Early effects include euphoria, muscular

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fasciculations or twitching discomfort in breathing speaking or swallowing blurred or double vision sensations of heat cold or numbness and sweating with higher levels in the blood extreme apprehension disorientation and convulsions may occur The latter are generally preceded by definite electroencephalographic changes. Finally with severe overdosage, cardiovascular depression and respiratory arrest occur due to medullary depression In anesthetized patients central nervous system toxicity and convulsions may not occur here the first manifestation of toxicity may be cardiovascular depression When anoxia is present, cardiovascular toxicity may also appear early Toxic hypotension secondary to lidocaine can be controlled with pressor agents

The cardiac effects of lidocaine have been studied in a relatively limited number of animal experiments. In dogs, blood pressure and cardiac output rise in response to the drug Presumably this is a result of stimulation of sympathetic centers, since vagotomy or decerebration blocked the changes In larger doses peripheral vasodilatation occurs, without a rise in central venous pressure Of 90 dogs in which ventricular fibrillation had been induced cardiac resuscitation with lidocaine was successful in a large number The results were good but somewhat less impressive in 46 hypothermic dogs treated with the drug The over-all conclusions from animal studies on lidocaine emphasized its apparent safety factor and demonstrated its effects on the cardiovascular system both by (1) directly suppressing or lowering the threshold for ventricular fibrillation and by (2) indirect stimulatory effects on the central nervous system

With this background the present indications for lidocaine in clinical cardiology have evolved In several large groups of patients undergoing cardiac surgery the drug has been given intravenously to anesthetized patients safely and effectively Lidocaine was of value in preventing converting or ameliorating mechanically induced arrhythmias during cardiac surgery Decreased ventricular irritability was noted within 45 to 90 seconds The duration of action was 10 to 20 minutes, and administration of the drug could be repeated without toxic effects. The use of lidocaine in unanesthetized patients with acute ventricular arrhythmias has been found to be equally effective and safe within proper dosage ranges. Although no allergic reactions have been reported as yet a history of severe allergies is a relative contraindication to the use of the drug Patients allergic to procaine may safely use lidocaine

When a new therapeutic agent is introduced a requisite is its distinct advantage over similar agents utilized successfully for longer periods of time. Such indeed seems to be the case with lidocaine. The drug in effective doses does not produce the electrocardiographic changes, falls in blood pressure and diminished myocardial contractility noted with procaine, procaine amide and quinidine.

For specific purposes, its superiority to procaine amide and quinidine lies in its brief duration of action and relative safety It is apparent that for long lasting effects, lidocaine is impractical except by constantly supervised intravenous administration It seems to be quite safe and effective in a single intravenous dose of 1 mg per kilogram Repeated doses may be given safely at 20-minute intervals to a maximum of approximately 750 mg

Lidocaine is contraindicated in patients with the Stokes-Adams syndrome with A-V *dissociation and a slow nodal or idioventricular* pacemaker as are other antiarrhythmic agents Further slowing of the pacemaker may produce a paradoxical increase in ectopic ventricular activity As with therapy of arrhythmias in general, prompt correction of anoxia pH abnormalities or irritating stimuli are necessary in order to prevent recurrences.

In summary lidocaine appears to be a highly effective agent for treating ventricular arrhythmias by intravenous administration Its use in cases of paroxysmal supraventricular tachycardia has been reported but not fully documented as yet. The drug seems to be particularly useful in patients undergoing surgery in areas near or involving the heart, where arrhythmias may be produced by an acute mechanical stimulus The use of lidocaine during cardiac catheterization for situations in which mechanical irritation has

produced arrhythmias would seem to be of great value. In patients with ventricular arrhythmias or prefibrillatory mechanisms secondary to acute cardiac crises, the use of intravenous or intracardiac lidocaine prior to, or in association with electrical defibrillation may prove to be invaluable.

*The use of intravenous lidocaine in treating arrhythmias, as of the time of this writing, is approved for investigational purposes only.

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Annotations

Steroids in myocardial infarction

In the 40 years that have followed the introduction of the electrocardiogram into clinical practice the frequency with which a diagnosis of myocardial infarction is made has multiplied at an alarming pace and much has been learned about the natural history of coronary artery disease. However the treatment of myocardial infarction as distinct from complications, such as thromboembolism, failure, and arrhythmias, has altered little over this period, and bed rest remains a cornerstone in early management.

The possibility that cortisone could have an effect on infarct size and the subsequent amount of myocardial scarring was raised by animal experiments, but when other workers failed to confirm these results, and the theoretical problems of poor healing and deficient scar formation were raised, the work fell into abeyance.

In 1954 Prinzmetal and Kennamer[3] showed that cortisone might abolish complete heart block and attributed this to an anti-inflammatory effect a conclusion which has been more recently supported in larger series by other workers.[4] In 1958 Gerlach and Compeau claimed to show increased vascularity of myocardium, decreased mortality and a smaller area of residual fibrosis when surgically produced infarcts in dogs were treated with a regimen of cortisone. On the basis of the results in a small controlled clinical trial they believed that cortisone might be valuable to combat shock, increase coronary collateral circulation, and decrease the size of the scar in the myocardium. In the same year Fiegel, in a review of the place of glucocorticoids in cardiology thought that the use of prednisolone in cases of acute infarction could reduce mortality and Kaiser[8] was of a similar opinion, particularly in the case of severe or prolonged shock in which he claimed that steroid therapy was a lifesaving measure.

Random controlled trials with oral prednisolone in acute myocardial infarction[-10] showed no beneficial effect. A further trial was reported wherein only severe cases of myocardial infarct were selected by means of the Coronary Prognostic Index,[11] using a high-dosage parenteral hydrocortisone regimen that started with 400 mg on the first day and then decreased progressively over 14 days. This showed improved survival against a calculated expected mortality.[12] Histologic examination of "treated" fatal infarctions in this trial, when compared with matched fatal untreated infarctions, appeared to show an anti-inflammatory effect in the infarct area with regression of the collar of cellular infiltrate and edema around the necrotic area. No tendency to cardiac rupture was found.[13] The evidence for an anti-inflammatory effect of the steroid was similar to that described by Johnson and associates[1] in animals.

In view of this gathering volume of evidence, a multicenter double-blind trial of hydrocortisone in cases of acute severe myocardial infarction was organized by the Scottish Society of Physicians.[14] Seventeen hospital medical units participated. For ethical reasons, a modified regimen, giving systemic hydrocortisone phosphate for 48 hours (400 mg in the first 24 hours) and the same drug orally in diminishing dosage for an additional 12 days was substituted. The trial using this predominantly oral regimen showed no difference in mortality between the treated and the control patients. Even in a proportion of patients with severe and persistent shock no difference was found between the hydrocortisone and the control group, the mortality in each being 62 per cent.

This negative result was in keeping with the observations of Klein and Palmer[15] who showed that in the presence of cardiogenic shock, the adrenal gland produced mean plasma cortisol levels some 3 to 17 times above normal values, and that, even in uncomplicated myocardial infarction plasma cortisol is increased 2 to 3 times normal. They also performed serial (seventh to twenty-first days) estimations of plasma cortisol in a small number of patients with myocardial infarction. Those shocked patients who died had a high initial elevation and in the 2 who survived the initial peak was followed by a rapid return to normal. Serial samples in 4 nonshocked patients showed no constant curve being lowest in 2 on the first day and rising thereafter and in the other 2 being highest on the first day and then falling to normal. In view of a seemingly adequate physiologic response from the adrenal cortex even in the nonshocked patients, these authors concluded that there is no justification for the use of cortisone in patients with myocardial infarction.

We must distinguish, however between physiologic and possible pharmacologic effects of steroids. In patients with bacteremic shock Lillehei and his colleagues[16] have found improved cardiac output and decreased peripheral resistance without depression of blood pressure or other ill effects when as much

as 2 Gm. of hydrocortisone is given intravenously in a few minutes. Indeed, they advocate this therapy in such patients in a dose of 15 to 25 mg. per kilogram of body weight ("up to several grams of hydrocortisone") until shock is remedied. Nor do they taper off the dosage.

Since these are massive doses when compared with anything already reported to be used in myocardial infarction, perhaps controlled clinical trials at these levels of dosage should be carried out, along with further histologic studies of infarcts, before the value of steroid therapy in patients with myocardial infarction is altogether dismissed.

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Diagnostic enzymology in myocardial infarction

The estimation of enzyme levels in human serum allows valuable confirmation of myocardial necrosis, particularly so when electrocardiographic confirmation is delayed or masked by bundle branch block, arrhythmia, or the changes due to previously healed myocardial infarction. The enzyme of choice should show a rapid rise to abnormal levels in all cases and remain elevated for a prolonged period. It should also be highly specific for myocardial damage, and, when estimated, the method should be both straightforward and inexpensive.

Serum glutamic oxaloacetic transaminase (SGOT), also known as aspartate aminotransferase, remains the enzyme of choice in most hospital laboratories. It rises to abnormal levels within 24 hours of the onset of symptoms, reaches a peak at 2 days, and returns to normal levels by about the 6th day. Significant elevations are reported in up to 97 per cent of cases of proved myocardial infarction, lower figures usually resulting from delayed estimation, the peak having been missed. The significance of marginal elevations can be difficult to assess when serial samples have not been studied. There is also a tendency to false-positive elevations in a variety of other diseases, particularly hepatitis. In myocardial ischemia without actual infarction the results are

conflicting but slight elevations have been reported. Congestive cardiac failure in itself has been reported to cause pronounced elevations.[3]

These disadvantages have led to the introduction of other enzymes as diagnostic aids. Serum creatine phosphokinase, malic dehydrogenase, aldolase, and phosphohexose isomerase show transient elevations similar to those of SGOT and offer little advantage, although creatine phosphokinase appears to have a high specificity for the myocardium. Serum lactic dehydrogenase (SLDH) levels remain elevated for 7 to 10 day after myocardial infarction, but this advantage is offset by poor specificity of this enzyme for the myocardium. Attempts to overcome this lack of specificity have included estimation of its isoenzyme pattern, the fastest moving component being highly specific for the myocardium. Since this component is also relatively heat stable, measurement of its heat-stability index[4] has been advocated and also its resistance to acetone precipitation. These procedures, however, are too laborious for routine use. This fast-moving isoenzyme possesses, in addition, activity against α-oxobutyrate, a property shared by an enzyme designated *hydroxybutyrate dehydrogenase* (HBD) by Elliott. The actual relationship between LDH and HBD is still unknown, but the value of the latter enzyme in the diagnosis of myocardial infarction is now established. Both spectrophotometric and colorimetric[4] methods for its estimation exist, and several studies have shown that SHBD levels rise to abnormal levels within 24 hours of the onset of myocardial infarction, reach a peak in 2 to 3 days, and return to normal in 10 to 15 days.

Different workers have reported slightly differing normal values for SHBD, probably reflecting differences in the type of "normal" subjects studied. A recent study in this hospital using the colorimetric method revealed a normal range in 52 blood donors of 42 to 106 units per liter (1 unit T. = 1 1 L. L. = 2 1 spectrophotometric units) with a mean of 75 units per liter and a standard deviation of 16 units per liter. This accords with the findings of Preston,[30] who used the same method, although other workers quote upper limits of up to 140 units per liter. This figure is usually accepted as that above which good correlation with electrocardiographically confirmed myocardial infarction can be obtained. With this level, SHBD estimations were performed in 100 cases of electrocardiographically confirmed myocardial infarction, and the levels were found to be elevated on day 1 in 64 per cent (86 per cent), on day 2 in 87 per cent (97 per cent), and on day 3 in 89 per cent (83 per cent). The figures in parentheses are those of Preston[30] using the same method. Eighty-nine per cent of the cases still showed elevated levels on the seventh day. Similar results have been obtained by other workers using the spectrophotometric method[31] and confirm the value of this test, especially in cases in which admission to hospital has been delayed for several days after the onset of symptoms. SGOT levels may rise to abnormal levels a few hours before SHBD levels do so, but in practice this has not been found to be a disadvantage.

Although normal SLDH levels have been reported in a number of cases of confirmed myocardial infarction,[30] there are few published cases of similar false-negative results with SHBD. For example, Rosalki[31] found elevated levels in 100 per cent of 330 cases of confirmed myocardial infarction. False-positive elevations can occur in a variety of diseases, notably megaloblastic anemia, leukemia, malignancy, and liver disease, but in general HBD has been reported to have a higher specificity for the myocardium than either GOT or LDH. In myocardial ischemia without actual infarction, Rosalki,[31] reviewing 129 cases, found 8 per cent with marginal elevations. In our own series of 40 cases of myocardial ischemia, only 1 case showed an SHBD level above 140 units per liter. Those cases with normal ECG tracings had SHBD values on the average 11 per cent lower than those cases with ECG changes of ischemia. In congestive cardiac failure, Preston found significantly raised levels in 5 cases of severe failure from a total of 30 cases, but other workers have found only borderline elevations in the occasional case. Marginal elevations also occur in occasional cases of pulmonary infarction but less frequently than with SGOT or SLDH.

SHBD elevation may be of some prognostic value in that a higher mortality rate has been reported in cases in which the peak elevation is abnormally high.[17] Persistent HBD elevation beyond 2 to 3 weeks may also occur with severe infarcts.[17]

Thus, SHBD appears to be a more specific, sensitive, and lasting parameter of myocardial infarction than either SGOT or SLDH. There are difficulties, however, in comparing the diagnostic efficiency of SHBD estimation with that of the ECG. It has been assessed that diagnostic ECG changes occur in only 82 per cent of cases of acute myocardial infarction subsequently proved by autopsy, and it is known that almost 100 per cent of cases confirmed by the ECG show elevated SHBD levels. But the percentage of cases of myocardial infarction, confirmed by autopsy, with SHBD elevation but without diagnostic ECG changes is still unknown. Now that a more specific enzyme assay for myocardial necrosis is available, it would seem to be important to determine its value as an absolute diagnostic criterion rather than as a mere supplement to the ECG, since it is in such cases of chest pain without ECG abnormality that the greatest diagnostic problem arises.

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Suicidal attempt by overdosage of ajmaline

Ajmaline, the therapeutic agent for cardiac arrhythmias, is a pure alkaloid isolated from Rauwolfia. It diminishes cardiac excitability, slows down the heart rate and increases the A-V conduction time. Numerous reports emphasize its value in the treatment of extrasystoles (auricular as well as ventricular), paroxysmal tachycardia, and ventricular tachycardia. Its toxicity is low. However accidental intoxications have been reported, particularly in children. We have observed a case of attempted suicide by ingestion of ajmaline.

The patient, a 24-year-old mechanic had been treated for about 10 years for repeated attacks of paroxysmal tachycardia. He stated that his attacks did not respond to digitalis, quinidine or procaine amide. Clinical examination, electrocardiogram and fluoroscopy were within normal limits. He weighed 70 kilograms and was 170 cm tall. The blood pressure was 120/80 mm Hg. However the patient behavior seemed to be unusual: he appeared to be dejected but not really depressed. A prescription was given for a daily intake of 150 mg and later 100 mg of ajmaline. The amount of medication necessary for a 3-week treatment was entrusted to the patient.

One evening 4 days later the patient was found unconscious in a telephone booth. He was immediately admitted to the Neuchâtel City Hospital, les Cadolles (Director Dr J. A. Barrelet), where he regained consciousness but remained in a state of shock: the pulse could not be felt, the blood pressure was 75/50 mm. Hg; there was cyanosis of the face, and the extremities were cold. A personal notebook found on the patient revealed that half an hour earlier he had ingested 2,240 mg of ajmaline. Fifteen minutes after the ingestion, the patient wrote down "I still do not feel anything in particular."

The blood pressure rose under treatment (continuous intravenous drip of 8 mg. of metaraminol in dextrose), but when the perfusion was slowed down, clonic-like generalized convulsions appeared accompanied by episodes of unconsciousness and apnea which required renewed application of artificial respiration. Permanent electrocardioscopic control showed no cardiac arrest.

An electrocardiogram recorded on admission showed a ventricular rate varying between 50 and 90 beats per minute, with periods of ventricular standstill lasting 1 to 2 seconds. The P wave was nowhere to be seen. The intraventricular conduction time increased: the QRS complex measured 0.28 second, and the Q-T interval 0.92 second. The electrocardiographic tracing became more and more chaotic (Fig

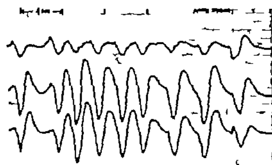


Fig. 1. Standard Leads I, II and III recorded 4 hours after absorption of 2,240 mg. of

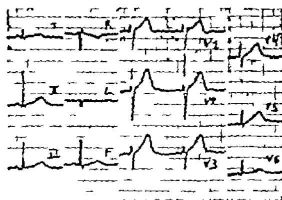


Fig. 2. The electrocardiogram had returned to normal 30 hours after the massive intake of ajmaline.

1. The QRS duration increased to 0.32 second and bouts of ventricular fibrillation appeared 4 hours after the beginning of intoxication. The patient then slowly calmed down. There was abundant diuresis. At the seventh hour, duration of the QRS complex was down to 0.16 second with a left bundle branch block pattern. Thirty hours after intake of ajmaline the electrocardiogram was normal (Fig. 2) and the patient had recovered. A psychiatric examination revealed that the patient had a severe neurosis, and that there had been three previous attempts at suicide.

Ajmaline, introduced by Kleinsorge[1] in 1959, does not have the sedative action of other Rauwolfia alkaloids. It has an inotropic effect that neither quinidine nor procaine amide has. However, its action on conduction should be kept in mind. The lengthening of intraventricular conduction up to 0.32 second was particularly impressive in this case of attempted suicide, and it confirmed the idea that ajmaline should be used with great caution in cases of bundle branch block and is contraindicated if serious conduction disorders are present.

The arterial hypotension and the severe state of shock observed in our patient occurred after ingestion of an amount 22 times superior to the therapeutic dosage (100 mg.) of ajmaline, in other words, 32 mg. per kilogram of body weight instead of 1.5 mg. per kilogram. A few cases of cardiac arrest or cardiovascular collapse have been reported after intravenous injection of ajmaline,[3] but this occurs most frequently in elderly patients. If this medication is to be used intravenously, i.e., in cases of refractory and ominous tachycardia, it should be injected slowly, 50 mg. in 5 or 10 minutes, with auscultatory and, if possible, electrocardiographic monitoring. A major analeptic agent should also be kept ready for use: Methedrine or metaraminol rather than noradrenaline, which alone can produce a ventricular tachycardia. In case of cardiac arrest or severe signs of intoxication, classic therapeutic measures must be employed for a rather long time in order to allow the elimination of ajmaline: perfusions to facilitate diuresis, restoration of blood pressure, and, eventually, thoracotomy and electrical stimulation of the heart.

When one considers the severe disorders of rhythm presented by this patient, the prompt restoration and complete recovery show that ajmaline is easily eliminated and that its toxicity is rather low.

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A new theory relating atherogenesis and coronary heart disease to impairment of plasma surface activity

A series of observations, originating in 1957, have led to a new theory which relates both atherosclerosis and coronary heart disease to impairment of the surface activity of plasma.[1-4] It appears to explain and integrate existing knowledge of these diseases more comprehensively than have previous hypotheses.

Circulating blood particles bear upon their surface

a negative charge of electricity. This charge is partly dependent upon the basic nature of the surface, but also upon substances adsorbed to that surface from the plasma. Such substances, capable of influencing surface electrical charge, are termed *surface active agents*. They will also be adsorbed by the inner lining of the blood vessel wall and influence its surface electrical charge. This negative charge borne by particles such as erythrocytes, platelets, chylomicra, fibrin, and by the inner lining of the vessel wall, will cause mutual repulsion and will be a factor not only in preventing aggregation but also deposition upon the lining of the vessel wall. It is to be expected that several substances dissolved in the plasma will be capable of surface activity. Their net effect can be measured by estimation of the size of the electrical charge borne by erythrocytes suspended in their own plasma. From theoretical considerations it might be suspected that in disease considered to be related to platelet aggregation and lipid or fibrin deposition a relatively low negative charge corresponding to a relative impairment of plasma surface activity would be found. Experimental observations[1-4] suggest that this indeed is the case, and reduced plasma surface activity has been demonstrated in coronary heart disease and other conditions related to atherosclerosis.

During study of the surface of human erythrocytes, suspended in their own plasma, it was noted that variations in charge did occur. The apparatus consisted of a small glass chamber containing the suspension which could be observed microscopically. When a small constant direct electrical current was passed through the plasma, the previously stationary erythrocytes moved toward the positive electrode impelled by their own negative surface electrical charge. Under constant conditions the time taken for one erythrocyte to move a certain distance was related to the size of its electrical charge and termed *the erythrocyte migration time* (E.M.T.), the relationship being an inverse one. Upon random sampling of hospital patients there appeared to be, upon first examination, an age relationship consisting of an increasing mean E.M.T. with advancing years. But further work and study of the diagnoses suggested that a greater mean E.M.T. in the 40-69 age groups, as compared with younger groups, could well be due to the presence in the sampling of patients with diseases related to atherosclerosis, and this was supported by the return to a smaller mean E.M.T. after 70 years. A tentative explanation of the data is that individuals with a greater E.M.T., and, therefore, impaired plasma surface activity, die relatively earlier, probably because of the development of diseases related to atherosclerosis.

Following this work an estimation of E.M.T. was made in patients who had recovered from myocardial infarction, and a comparison was made with matched controls showing no evidence of atherosclerotic disease. A significantly greater E.M.T. was found in the patients with myocardial infarction. Further studies confirmed this and showed that prolongation of E.M.T. was consistently of a higher order of significance than was an increase in the level of serum cholesterol. The observations suggested that an increase in E.M.T. is more closely related to the etiology of coronary heart disease than is an elevated serum cholesterol, and it follows that it is a better single index in the investigation of this disease. It was also found that the myocardial patients with the lowest levels of serum cholesterol were those with the greatest E.M.T. and, conversely, that those with the highest levels of serum cholesterol had the least increase in E.M.T. from the normal. An inverse linear relationship was demonstrated between these two indices. Myocardial infarction was found to be related to the attainment of a certain critical constant that incorporates these two indices. However, no relationship was found between the two indices within the individual patient. The evidence suggested that they were two independent factors. The anomalies of the theory relating the development of coronary heart disease to an increase in the level of serum cholesterol are explained by the greater deficiency in plasma surface activity. The two indices mutually support each other, and this is demonstrated by the efficient segregation of patients with myocardial infarction from controls when the indices are used in conjunction. It would appear that therapy should be directed to reducing both serum cholesterol and E.M.T., but measures to reduce one or the other factor should only be adopted when it is known that they do not cause an increase in the other.

It has been shown that variations in E.M.T. are accompanied by corresponding fluctuations in the migration time of chylomicra measured in a similar manner. This indicates that variations in plasma surface activity affect such dissimilar particles as erythrocytes and chylomicra in like manner, and that E.M.T. is inversely a measurement of the colloidal stability of circulating lipid. If platelets and leukocytes are present with erythrocytes during the measurement of E.M.T., it will be seen that they also appear to move at a similar rate, which suggests that their surface electrical charges are likewise modified by alteration in the surface activity of plasma. A basis is now provided for reconciling and combining the lipid and thrombogenic hypotheses into the single new theory relating atherogenesis and coronary heart disease to deficiency in plasma surface activity. The lipid hypothesis implies that in some way lipid accumulates in the vessel wall as the result of transference from the circulating blood. There is considerable evidence, which cannot be reviewed here, to support this theory. The importance of plasma surface activity in such a mechanism has not previously been recognized. The lipid hypothesis does not satisfactorily explain or incorporate the evidence which has led to the thrombogenic hypothesis of atherogenesis or the thrombus formation in coronary occlusion. This is provided by the new theory. The thrombogenic theory relating coronary heart disease and atherosclerosis to thrombus formation and organization with endothelialization of mural thrombi embodies physical mechanisms which are examples of the aggregation and deposition of particulate matter, and in which plasma surface activity will be of major importance. It will be expected to influence such factors as platelet stickiness, adhe-

aggregation, fibrin formation, and the deposition of thrombi. The lipid and the thrombogenic hypotheses can be incorporated into one concept, and the evidence previously leading to two conflicting hypotheses can be related to the effect of the common factor namely deficiency of plasma surface activity

Problems due to surface activity phenomena are encountered in the oil industry Pipelines carrying oil containing particles in colloidal state become occluded due to the aggregation and deposition of these particles. This deposition occurs excessively where centrifugal forces operate. Because of this it is found on the outer arc of a curved pipeline or at the orifice of a minor pipeline branching off from the main system. The rate of flow is also of considerable importance, in that reduction will facilitate settling on the walls. This deposition is, in practice, minimized by the addition of surface active agents. In the human arterial system, we have a dynamic fluid system carrying colloidal and particulate matter The curved arch of the aorta and the orifices of the intercostal arteries are common sites for involvement, as is the coronary arterial system, which is unique in that the rate of flow is greatly reduced with each ventricular systole. It is possible that the surface activity theory of atherogenesis and coronary heart disease offers an explanation for the striking and puzzling focal distribution of the lesions

If plasma surface activity deficiency explains facts which previously could not be integrated into one theory It is logical to seek the chemical substances of the plasma that are responsible for this physical defect This has led to a recently published preliminary communication on a plasma protein abnormality related to myocardial infarction, apparently involving 7S gamma globulin. Further work now in progress is encouraging

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Letter to the Editor

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To the Editor

In his recent publication on acute nonspecific pericarditis, Dr Liu implied that the disease is no longer benign when it occurs in a patient with pre existing myocardial damage.[1] His statement was based on a review of 12 fatal cases from the literature, including his own.

In contradistinction to this report, we had the opportunity to observe acute nonspecific pericarditis in a 10-month-old child in whom the outcome was fatal, and in whom there was no previous cardiac damage. Our young patient was hospitalized for congestive heart failure of 3 days duration, with the clinical, electrocardiographic and radiologic evidence of acute pericarditis. Later on, the clinical course was complicated by pericardial tamponade. A sanguinolent pericardial tap relieved the tamponade, and the cardiac failure gradually subsided, only to return during the third week after admission. The child died suddenly on the twenty-fifth hospital day Necropsy revealed severe adhesive fibrous pericarditis with acute and chronic inflammatory changes. Diffuse interstitial lymphocytic and histiocytic infiltration was present The virological studies were not contributory

We tend, also, to disagree with Dr Liu that the incidence of fatal arrhythmias is increased *in* patients with pericarditis with additional myocardial damage. In a large number of patients with acute nonspecific pericarditis, we observed that the death rate due to congestive heart failure was 3.2 per cent. Arrhythmias were not recorded in this large group.[2]

It seems to us to be justified to assume that preexisting myocardial damage may be of importance only in the elderly However our experience, as well as that of others, suggests that the degree of the concomitant myocardial involvement in acute nonspecific pericarditis is the most significant factor determining the prognosis for the patient.[4-7]

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Book reviews

HUMAN FETAL AND NEONATAL CIRCULATION. By John Lind, M.D. Professor of Pediatrics, Karolinska Institute Co-Director Wenner-Gren Research Laboratory Stockholm Sweden Leo Stern, M.D. McGill University Montreal, Quebec and Carl Wegelius, M.D. Director Wenner-Gren Research Laboratory Stockholm, Sweden. Springfield, Ill. 1964 Charles C Thomas, 54 pages, 93 illustrations Price $5.75

This short monograph discusses and clearly illustrates many of the marked anatomic and physiologic vascular changes which occur in the human fetal and neonatal periods. In the first part of the book, fetal circulation is portrayed by the use of direct angiocardiography in fetuses of 12 to 20 weeks gestation. The second part deals with the onset of extrauterine life establishment of pulmonary respiration, circulatory dynamics of lung expansion, the ensuing changes in the heart and main vessels, and dynamics of the neonatal heart. The roentgenograms, angioradiograms, and diagrams are most instructive. Electrocardiographic tracings accompany many of these. Each of the two sections contain general outlines supported by detailed analysis of the anatomy of the circulatory system and its functions. This well-written book should be of use to anyone interested in problems concerning the normal and abnormal development of the cardiovascular system.

RHEUMATIC FEVER. DIAGNOSIS, MANAGEMENT AND PREVENTION. By Milton Markowitz, A.B., M.D. and Ann Gayler Kuttner, B.S., Ph.D., M.D. Sinai Hospital of Baltimore, Baltimore, Md. Philadelphia 1965 W. B. Saunders Company 242 pages Price $7.50

This is the fifth of a series of monographs on major problems in clinical pediatrics. The authors briefly discuss the changing patterns of rheumatic fever, the biology of group A beta hemolytic streptococcus, etiology, pathogenesis, pathology, clinical manifestations, laboratory findings, treatment, chronic heart disease, criteria for diagnosis and many other aspects of rheumatic fever. A good bibliography is appended to the book. The presentation is clear and well organized. Obviously the authors could not be too extensive in their presentations in such a short book, but that is an advantage to the average busy reader. A bibliography is available for more detail in the follow-up of aspects of rheumatic fever. The section on chronic heart disease is not very good. For example the discussions on the roentgenographic findings and the electrocardiogram require that one have a thorough knowledge of these two subjects in order to appreciate the significance of the brief remarks, and if the reader is so well informed, these discussions are useless and inadequate. Nevertheless the student and physician will find this to be a good book.

NERVOUS CONTROL OF THE HEART. Edited by Walter C. Randall, M.D. Baltimore, 1965 Williams & Wilkins Company 251 pages. Price $11.95

This is a compilation of papers presented at an afternoon session held during the Annual Spring Meetings of the American Physiological Society in 1963. The book is dedicated to the late Dr. Carl Wiggins. The nine contributors to the book write about past and present hypotheses of cardiac control intracranial representation of cardiac innervation anatomy of central neural pathways influence of autonomic activity terminal innervation to the heart, atrioventricular responses to sympathetic nerve stimulation, and sympathetic influences on the synchrony of myocardial contraction. Each chapter represents a summary of the respective author's studies and his impressions of the literature. There are several illustrations, and a bibliography is included at the end of each paper. If any discussions of the papers were presented, the book does not indicate it; this is unfortunate. As in the case of all symposia, this is an incomplete summary of an important subject. Nevertheless, it is a useful book and worth one's reading in order to learn some of the present ideas on the subject.

BASIC CARDIOLOGY. By T. E. Gumpert, M.B., Ch.B. (Sheff.) F.R.C.P. (Lond.) Lecturer in Medicine and Cardiology University of Sheffield, Sheffield, England. Second edition, Baltimore 1965, Williams & Wilkins Company 234 pages. Price $9.75.

This is a series of lectures for medical students. "Elementary Cardiology" would be a more appropriate title. Covering the entire field of clinical cardiology including electrocardiography, cardiac catheterization, and angiocardiography in a small book requires extensive abbreviations. For medical students it does provide a very clear survey of clinical cardiology.

Even for a cardiologist, it hardly seems to be appropriate to teach a student to begin a physical examination with the chest and heart. A student should be taught the importance of a history and

physical examination before learning how to read an electrocardiogram. The latter is presented in the second chapter. It would seem to be appropriate to present cardiac murmurs before the seventeenth chapter. The early manifestations of the various types of heart disease should be considered before the manifestations of heart failure.

There are numerous misleading statements. Indicating that calcification and gross cardiac enlargement contraindicate mitral surgery and that there is no satisfactory surgical operation for mitral regurgitation is misleading. Breathlessness does not limit exertion in all except the mildest cases of mitral regurgitation. Clinical cyanosis is not a constant feature of right-sided heart failure. Percussion of the lower border of the liver is not happily reliable. Frank jaundice suggests a pulmonary embolus rather than simple right-sided heart failure. Prostatic obstruction does not precipitate heart failure, although the two may occur together. Right bundle branch block is not almost invariably present in atrial septal defects.

Despite numerous similar aberrations, these are very satisfactory lectures for a medical student.

Books received

ARTERIAS SUPRA AORTICAS. By Alvaro de Paulo Pontes, Rio de Janeiro, 1963, University of Brazil, 316 pages.

THE HEMATOCRIT IN CLINICAL PRACTICE. By Solomon N. Albert, M.D., Sumer Chand Jain, M.B., B.S., Jo Shibuya, M.D., D.M.S., and Chalom A. Albert, M.D. Springfield, Ill., 1965, Charles C Thomas, 74 pages. Price $4.75.

AN INDEX OF RESPONSES TO THE GROUP RORSCHACH TEST. STUDIES ON THE PSYCHOLOGICAL CHARACTERISTICS OF MEDICAL STUDENTS. II. By Caroline Bedell Thomas, Donald C. Ross, and Ellen S. Freed, Baltimore, 1965, The Johns Hopkins Press, 302 pages. Price $15.

RADIOACTIVITY IN MAN. Edited by George R. Meneely and Shirley Motter Linde. Springfield, Ill., 1965, Charles C Thomas, 616 pages. Price $24.50.

SURGERY IN WORLD WAR II. THORACIC SURGERY. VOL. II. Edited by Arnold Lorentz Ahnfeldt. Frank B. Berry, and Elizabeth M. McFetridge, Washington, D.C., 1965, Office of the Surgeon General, 615 pages. Price $7.25.

THE WORKS OF WILLIAM HARVEY, M.D. By Robert Willis, M.D. New York, Johnson Reprint Corporation for the Sydenham Society, London, 617 pages. Price $25.

MODERN TREATMENT. Vol. 2, No. 4. Treatment of Diabetes Mellitus, edited by Thomas F. Frawley, M.D. Emergency Treatment of Trauma, edited by Henry C. Cleveland, M.D. New York, 1965, Hoeber Medical Division, Harper and Row. Published bi-monthly by subscription only. $16 per year.

HOMER WILLIAM SMITH, Sc.D. HIS SCIENTIFIC AND LITERARY ACHIEVEMENTS. Edited by Herbert Chasis, M.D. New York, 1965, New York University Press, 282 pages. Price $4.

Announcements

DEDUCTIVE ELECTROCARDIOGRAPHY The Division of Continuing Education of The University of Texas Graduate School of Biomedical Sciences at Houston will present course on Deductive Electrocardiography on Dec 6-10 1965 in the Texas Medical Center Houston Texas.

This course which will be presented by the celebrated electrocardiologist, Dr Demetrio Sodi Pallares, of Mexico City will include basic concepts of the anatomy chemistry and physics of the heart muscle during rest excitation, and relaxation, in addition to a thorough discussion of electrocardiographic patterns occurring in various clinical states.

For further information, write Division of Continuing Education The University of Texas Graduate School of Biomedical Sciences at Houston, 102 Jesse Jones Library Bldg Texas Medical Center Houston, Tex. 77025

The Third Annual Seminar in Cardiology DIAGNOSIS AND MANAGEMENT OF CARDIAC ARRHYTHMIAS, sponsored by the H Milton Rogers Foundation for Heart Research, will be held at the Tides Bath Club Redington Beach, St Petersburg, Fla., Thursday Dec. 9 through Sunday Dec 12 1965.

The faculty will include Harold H Bix, M.D Baltimore Md Agustin Castellanos, Jr M D Miami Fla Charles Fisch, M D Indianapolis, Ind Albert D Kistin, M D., Beckley West Virginia and Frank LaCamera, Jr., M D St Petersburg Fla and will be directed by Henry J L Marriott, M D St. Petersburg Fla.

Registration is limited to 100

For further details write to The H. Milton Rogers Foundation for Heart Research, 500 First Federal Bldg St Petersburg Fla

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Editorial

The place of anticoagulants in the treatment of cerebrovascular disease

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In this scientific era in medicine, it is a most remarkable paradox that the role of anticoagulant therapy in occlusive vascular disease is still undetermined after 17 years of clinical application.

This unusual situation merits examination. The initial use was based upon the naive hypothesis that since vascular occlusions are sometimes thrombotic, anticlotting drugs should be of therapeutic value. Only in recent years, after numerous papers reporting uncontrolled or inadequately controlled results, has the situation been more critically examined.

In the first place, anticoagulants do retard the clotting of blood in vitro. This process is, however, entirely different in its genesis from intravascular thrombosis occurring in vivo. Blood clotting mechanisms do form a part of the process of intravascular thrombosis, but to what extent anticoagulants affect this process—if at all—is quite unknown.

Secondly, it has been shown by Hutchinson and Yates[1] that only a small proportion of patients suffering from cerebrovascular disease showed evidence of thrombosis in intracranial or extracranial vessels at postmortem. Therefore it is clear that the treatment of a group of such patients will in fact include a large number who have no pathologic thrombus in their cerebral vessels. Many of these patients probably have repeated episodes of microembolization of their cerebral vessels to account for their ischemic attacks,[2] and the influence of anticoagulants on such a process is still unknown.

Thirdly, it is likely that any clinically useful action of the coumarin indanedione drugs is likely to be related to their action on blood clotting factors IX and X, yet the control of the drug dosage is commonly based upon a separate action on prothrombin and factor VII.

From these and many other considerations, it will be apparent that the use of anticoagulants is full of inconsistencies and illogicalities. Use of these drugs can be justified only by the results of clinically controlled trials demonstrating a superiority which outweighs any hazards of the therapy. Trials employing the patient as his own control are unsatisfactory; so too are trials using one type of treatment for X years, and another type of treatment or placebo for Y years, the two periods being sequential.

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From the results of the trials of Hill Marshall and Shaw[3,4] Barham Carter[5] and the collaborative trials in the U.S.A. reported by Dr. Miller Fisher,[6] it is clear that anticoagulant therapy offers no benefit to the patient with a completed stroke or nonembolic cerebral infarct. On the contrary the risks of cerebral hemorrhage in such a patient are considerable. In the early treatment of acute embolic cerebral infarction anticoagulants are dangerous because the pathologic process is almost always a red or hemorrhagic infarct. An important report by Ushiro and Schaller[8] records the presence of recent antemortem thrombi in 2 of 4 patients given anticoagulants in their trial. This finding they suggest implies that prolongation of prothrombin time (in the therapeutic range *in both patients) is not of itself sufficient* to prevent intravascular blood clotting.

The evidence for the efficacy of anticoagulants in patients suffering from transient cerebral ischemic attacks (T.I.A.) is not conclusive. Siekert and associates[7] reported *that only 4 out of 115 patients* had continued to have attacks after treatment was begun. Fisher[6] claimed similar results in 14 patients. Thirty two patients with transient cerebral ischemic attacks were reported by Fisher[6] and improvement was claimed *for the therapy. However all* of these reports are open to criticism on the grounds of (1) inadequate control of the trial (2) obvious bias of the author as witnessed by transfer from control to anticoagulant group and (3) difficulty in assessing the results of therapy—particularly if one patient experiences 30 attacks per week and another only 1 attack per year which inevitably is confusing in the statistical analysis of the results.

A little more information is available from two recently published trials.[11] In the first it was shown that withdrawal of anticoagulant therapy from 13 patients with transient cerebral ischemic attacks was followed by a recurrence of attacks in 8 patients only 2 of 13 matched patients who continued therapy had a recurrence. It is difficult to agree with the conclusion that this confirms the value of anticoagulant therapy in reducing the incidence of T.I.A., since the situation imposed is entirely artificial. Furthermore it is totally illogical to assume that since withdrawal of treatment X leads to the development of symptom Y then the use of X in a patient suffering from symptom Y will abolish that symptom.

Pearce Gubbay and Walton[11] report a small but strictly controlled trial in 37 patients treated for 11 months. Fifty-nine per cent of the treated group and 45 per cent of the controls had one or more additional T.I.A. Ninety-one per cent of patient months in the treated group and 88 per cent of patient-months in the control group were free of ischemic attacks after the trial was begun. One treated and 2 control patients developed a completed stroke during the period of observation. Small differences were apparent between patients suffering from vertebrobasilar insufficiency but the number of *patients was too small to attempt any* analysis of these differences.

It is apparent that there are considerable difficulties inherent in the assessment of anticoagulant drugs in patients suffering from cerebral ischemic attacks. However in view of the relatively good prognosis reported[12,13] in these patients (provided that they are not suffering from extensive occlusive vascular disease) it is very difficult to justify the widespread administration of anticoagulants.

Even if by more extensive trials it can be shown that any benefit accrues from their use such advantage would certainly be a minimal one, and outweighed by the hazards of hemorrhage drug rashes and nephropathy.

At the present time most physicians will concur with the conclusion of Mitchell and Schwartz in their excellent monograph[14] that "considered over-all, anticoagulants have proved less valuable in the management of arterial disease than was originally anticipated. What we urgently need is a drug which will alter the adhesiveness of platelets to each other." To this might be added the necessity for further investigations of thrombolytic and fibrinolytic drugs and the assessment of the role of surgery in carefully selected patients.

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Clinical communications

The hemodynamics in ventricular septal defect in childhood

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The prognosis in cases of isolated ventricular septal defect, and the indication for surgical closure are subjects for concern and are still matters of considerable doubt. A recent review[1] has suggested that the over-all picture is a benign one, that the main hazards to life are congestive heart failure and bacterial endocarditis and that early surgery to forestall progressive pulmonary vascular obstruction is rarely indicated. This approach has been emphasized by Arcilla,[2] Lucas,[3] and Lynfield[4] and their colleagues; on the other hand, Auld[5] and Weidman[6] and associates have indicated that a progressive increase in pulmonary vascular obstruction will occur early in some cases.

A series of 151 infants with ventricular septal defects who were catheterized before their first birthday has recently been reported from this department;[7] this demonstrated that most of the patients in this age group had large shunts (78 per cent) and serial studies suggested that a proportion of the infants who initially had large shunts developed progressive pulmonary vascular obstruction—the so-called Eisenmenger reaction—early in life.

The hemodynamic data from 247 additional patients who were catheterized in this laboratory between the ages of 1 and 16 years have subsequently been analyzed and the results are reported here. In some places the data from the "infancy" groups are included to obtain an over-all picture of 398 cases from birth to 16 years of age and an additional 25 cases which have been studied serially are added to the 25 previously reported. A comparison is made of the hemodynamics in the under 2 year and the 2 to 16-year age group.

Methods and materials

Routine catheterization procedures were used. All but the very young were lightly sedated with chlorpromazine, meperidine, and promethazine (CM[3]).[8] Pressures were obtained using Statham P23Db strain gauges at a reference level one third of chest thickness below the sternum and were recorded on a Sanborn 4-channel direct writer recorder and later on an

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Table I. Definition of hemodynamic groups and their frequency

Group	Pulm./Syst. flow ratio	Syst./Pulm resistance ratio	Patients 1 to 16 yr	Patients under 1 yr (Kidd et al 1965)	Total number of patients 0 to 16 yr
I	<2:1	Normal	99	(24)	123
II	>2:1	>7:1	56	(60)	116
III	>2:1	5:1–7:1	29	(29)	58
IV	>2:1	<5:1	37	(29)	66
V	<2:1	High PVR	5	(9)	14
VI	Reversed shunt	High PVR	21	(0)	21
			247	(151)	398

Electronics for Medicine DR8 recorder. Oxygen saturations and contents were assessed using a Wood oximeter and Van Slyke analysis. Oxygen consumption was calculated in all instances, using a figure of 180 mL. per square meter per minute.[9] The pulmonary artery was entered in all cases. *Total* pulmonary vascular resistance was calculated throughout: calculations using pulmonary perfusion pressures in those cases in which it was available showed some alteration in absolute values, but little change in intragroup relationships. In some cases either the systemic arterial pressure or the systemic oxygen saturation was not recorded, or both were not. Cuff pressure

(mean $\frac{S + 2D}{3}$) was used where necessary;

oxygen saturation was assumed to be 95 per cent unless pulmonary hypertension was present, or sedation was noted to be heavy and systemic desaturation was considered to be a possibility. All patients in whom the hemodynamic data were inadequate or suggested a possible associated lesion were excluded from the study. Data were entered on IBM punch cards, and calculations and analyses were made by the IBM 7094 computer[*] using conventional Fick formulae.

Results

Data from a total of 247 patients were adjudged to meet satisfactory criteria and were included in the study. The age incidence of the catheterized material is illustrated in Fig. 1. Over 30 patients were investigated in each of the second to the sixth years, and thereafter the number studied in any one year group fell below 15.

Hemodynamic classification. The material was divided into hemodynamic groupings as set out in Table I. In Group I were patients who had a low pulmonary/systemic flow ratio (FR) (less than 2:1) with normal pulmonary arterial pressures: the small size of the shunt was determined by the small size of the defect. Ninety-nine of the total 247 patients fell into this group. One hundred and twenty-two patients had high pulmonary blood flows (FR > 2:1) and these were classified into Group II: those with low pulmonary vascular resistance (PVR) systemic/pulmonary resistance ratio (RR) greater than 7:1; Group III: those with normal PVR (RR 5:1–7:1); and Group IV: those with higher PVR (RR < 5:1). There were 56, 29, and 37 patients in these groups, respectively. Group V included those patients with small shunts (FR < 2:1) due to increasing pulmonary vascular obstruction (5 patients) and Group VI comprised those 21 patients who at the time of study had clear evidence of shunt reversal due to vascular obstruction.

Age incidence in hemodynamic groupings. When the cases were set out in the hemodynamic groups by year of age at study, it became obvious that those patients in the second year of life (28 patients) had a distribution almost identical with those in the first year, whereas the distribution in the

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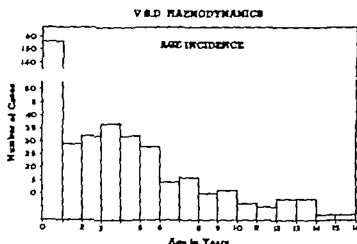


Fig. 1. Age distribution of patients at time of cardiac catheterization.

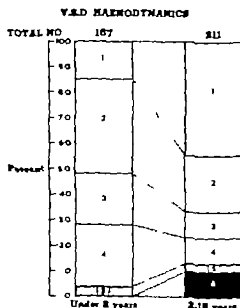


Fig. 2. Distribution of hemodynamic groups in age periods, under 2 years and from 2 to 15 years.

third and each succeeding year was similar.

Fig. 2 illustrates the hemodynamic groupings in the two age periods, under 2 years and 2 to 16 years. It will be seen that, whereas 78 per cent of those catheterized early in life had large shunts, only 40 per cent of those catheterized later fell into these groups. The difference is accounted for by the larger number catheterized later who proved to have small defects (Group I) and those who had reversed shunts (Group VI), none of whom were found at early catheterization. The differing indications of catheterization preclude interpretation of these data as demonstrating a trend with age.

Serial catheterization. A total of 50 patients have now undergone a second catheterization, 1 to 9 years after the first. In 9 patients the second study was made after surgical closure of the defect. Fig. 3 illustrates the change in mean pulmonary arterial pressure, together with the change in pulmonary/systemic flow ratio in 41 patients, 36 of whom were first studied when they were under 2 years of age. It was found that there was functional closure of the defect in 6 patients, all of whom had had large shunts at the time of the first study. In an additional 8 patients a fall in flow ratio, together with a fall in pulmonary arterial pressure, suggested that the defect had decreased in size. Four patients showed a drop in PVR, 15 patients had maintained their status, and 8 patients showed an increased resistance. It should be emphasized that in the large majority of those patients studied twice, the hemodynamic changes were slight.

Table II presents the detailed hemodynamic data in the 8 children who demonstrated the Eisenmenger reaction. It will be seen that all cases fell into the high flow groups at the time of the first study (mean pulmonary/systemic flow ratio 4.2:1—range 2.1-6.4). The second study was carried out at varying intervals after the first

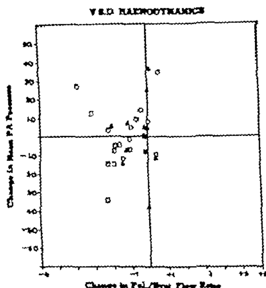


Fig. 3. Change in pulmonary/systemic flow ratio plotted against change in mean pulmonary arterial pressure between first and second cardiac catheterizations. The symbols refer to the hemodynamic group into which the case fell at first study. *Solid squares* Group I. *Open circles* Group II. *Open squares* Group III. *Open triangles* Group IV. *Solid circles* Group V.

(mean 3-1/12 years—range 1-3/12 to 5-3/12 years) and in each instance the systemic/pulmonary resistance ratio had decreased markedly (PVR increased). These ratios are independent of the calculated oxygen consumption and derive solely from the measured pressures and oxygen saturations.

Of the 9 patients who were restudied after surgical closure of the defect, in 4 the pulmonary arterial pressure had risen above preoperative levels. In one of these patients, it continued to rise and a third study when the child was 7 years old showed a pulmonary arterial systolic pressure of 130 mm. Hg (systemic pressure 94/58 mm. Hg) although the defect had been closed when the child was 25 months old.

Discussion

The present report brings to 398 the total number of cases of ventricular septal defect with adequate hemodynamic data reported from this laboratory. It should of course be realized that this is a selected group of patients and is not a typical cross section of the total population with ventricular septal defects, in approximately 1,200 of whom a diagnosis has been made clinically in this department. These patients were catheterized because of the severity of the lesion, in order to make a diagnosis or to determine the level of the pulmonary vascular resistance. Furthermore, the indications will vary with age; those with large defects tend to get into difficulty early and are catheterized in infancy, whereas those with smaller defects are regarded with less urgency and are catheterized when surgical closure is proposed at a later age. Conclusions as to the course of the hemodynamic changes, therefore, can only be based on serial study; however, the patients who have undergone two catheterizations are even more selected and cannot be considered to be representative of the large body of those with clinically diagnosed ventricular septal defects, the majority of whom have not been catheterized because their defects are thought to be small and hemodynamically insignificant. A clinical, radiographic, and electrocardiographic survey of the whole group is in progress and will be reported subsequently.

However, some conclusions can be drawn from the data of this catheter laboratory population. Among the points of interest are the large proportion (78 per cent) of children who had large pulmonary blood flows (FR > 2:1) when catheterized before the age of 2 years (Fig. 2). In the 2- to 16-year age group this proportion (Group II, III, and IV) was much smaller and cases of unequivocal shunt reversal (Group VI) were found for the first time. It would seem to be unlikely that these patients were in this state from the time of birth, since (a) no cases have been recognized in a catheterized series of 187 infants and (b) those with increased resistance (Group V) at first study have been found to have a drop in resistance with time, and those developing the Eisenmenger reaction (Table II) all had high flows previously. If such "congenital" cases exist, they must be exceedingly rare.

Since the changes can occur early in life it is obvious that any study which includes only catheterization data from children surviving infancy or over 3 years of age

Table II Hemodynamic data from serial cardiac catheterization of 8 children who demonstrated

Patient	Age (yr.)	Surface area (sq. M.)	O_2 saturations (%)			Pressures (mm. Hg)	
						PA	
			MV	PA	SA	Phasic	Mean
1	3/12	25	55	89	95	65/30	42
	4-10 12	68	61	69	86	110/65	85
2	4/12	24	53	90	98	40/15	23
	4-7 12	61	47	76	95	75/25	50
3	8/12	26	69	81	92	65/20	45
	6-1/12	54	58	60	73	100/55	70
4	1/12	22	58	88	95	49/13	28
	1-4 12	36	57	78	97	58/25	40
5	1-6/12	46	50	77	95	35/10	18
	3-2 12	60	65	73	90	80/30	54
6	1/12	25	55	83	92	66/30	45
	1-10 12	50	70	83	95	78/28	50
7	3 12	26	72	83	89	72/30	48
	2 5/12	48	58	71	88	75/48	55
8	3/12	27	64	86	93	60/20	35
	3-9/12	68	69	84	97	80/38	57

MV Mixed venous sample—RA or $\frac{(SVC+2\ IVC)}{(\ \ 3\ \ )}$ *PA* Pulmonary artery *SA* Systemic artery—aorta, brachial, or femoral. ... monary systemic flow ratio *RR* Systemic/pulmonary resistance ratio.

will obtain a distorted picture of the hemodynamics in this condition.

Thus, it has been suggested that low flow–high resistance cases are those in which there is risk from the Eisenmenger reaction if indeed it is not congenital.[7,14,20,21] However it is clear that if these patients had been catheterized for the first time in infancy they might then have demonstrated a high flow and moderate or low resistance phase. If they are studied for the first time at the age of 4 or 5 years, only the end-stages of the evolution may be seen and unjustified conclusions drawn. This is obviously an important point in a consideration of the management of children with this condition.

If progressive pulmonary vascular obstruction can develop early—and we have found cases in which there was increasing PVR by the age of 2 or 3 years—then surgery would seem to be indicated *in these cases* at an early age. Even then it is possible that this may be carried out too late since evidence is presented of progressive obstruction after closure of the defect.

Surgery may lead to an earlier death than would be the case were the defect left unclosed since the Eisenmenger patient may survive for 10 to 30 years, cyanosed but fairly active. We believe that a close watch should be kept on patients with a ventricular septal defect who have a high pulmonary blood flow in infancy and serial studies should be made when indicated. Those cases in which the pulmonary vascular obstruction is increasing should be defined and the patient slated for early operation.

progressive pulmonary vascular obstruction

Pressures (mm. Hg)		PBF/M (L./min.)	SBF/M² (L./min.)	TPVR/M² (dynes sec cm.⁻⁵)	TSVR/M² (dynes sec. cm.⁻⁵)	Pulm./Syst FR	Syst./Pulm RR
SA							
Phasic	Mean						
75/50 110/75	58 90	16 94 4 62	2 75 4 87	197 1 472	1 694 1 478	6 2 95	8 6 1 0
80/50 100/75	60 83	16 83 5 57	2 63 2 86	109 733	6 110 2 322	6 4 1 9	16 6 3 2
80/45 100/70	55 85	8 14 2 40	3 89 5 56	442 2 331	1 129 1 221	2 1 43	2 6 52
89/41 104/60	54 75	10 60 6 43	2 0 3 06	211 497	2 152 1 963	5 3 2 0	10 2 3 9
90/55 120/80	61 90	5 92 6 34	2 37 4 44	242 680	2 260 1 619	2 5 1 4	9 1 2 4
90/42 105/50	51 68	12 04 9 91	2 93 4 66	299 403	1 392 1 166	4 1 2 0	4 7 2 9
90/50 102/52	63 69	18 06 7 39	6 19 4 19	212 595	813 1 318	2 9 1 8	8 8 2
70/45 90/54	55 67	16 74 9 47	4 35 4 50	167 481	1 015 1 190	3 9 2 1	6 1 2 5

PBF and SBF: Pulmonary and systemic blood flow. TPVR and TSVR: Total pulmonary and systemic vascular resistance. FR: Pul-

Summary

(1) Hemodynamic groups are defined and the frequency in a catheter laboratory population of isolated ventricular septal defects is described. The cases of 247 patients 1 to 16 years old are analyzed and considered together with 131 previously presented cases of patients under 1 year of age. (2) A natural history is suggested the majority of septal defects are benign some defects get smaller or close a few patients develop progressive pulmonary vascular obstruction. (3) The pulmonary vascular obstruction may progress after surgical closure of the defect. (4) No congenital Eisenmengers were found. (5) Those who developed progressive pulmonary vascular obstruction had greatly increased pulmonary blood flow early. (6) It is recommended that a careful watch be kept on "high-flow" patients in the first few years of life and that they be restudied early to pick out the developing Eisenmenger reaction, with a view to prompt operation.

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Aids to electrical diagnosis of pacemaker failure

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The electronic pacemakers used in the therapy of atrioventricular block are still far from perfect. With a considerable percentage of them we must face the sometimes grave emergencies in patients returning with pacemaker failure. Proper treatment of this condition is based on the correct diagnosis of its cause. However, a complete set of diagnostic rules for the analysis of pacemaker failure is not yet available. Only a very few studies[1,2] have concentrated on this subject. It is the purpose of this paper to present experience with a few diagnostic methods which have proved to be helpful in solving some of the electronic riddles of this new syndrome. These will be presented in a systematic form followed by some summaries of cases in patients during treatment of whom this system gradually evolved.

Methods

1. Prefailure documentation of the pacemaker function. Analysis of pacemaker failure is greatly facilitated by comparing the postfailure clinical and electrical symptoms with records of the prefailure function. Pacemaker failure is frequent enough to warrant documentation of the prefailure status in every case. This applies both to the function of the pacemaker proper and to the patient-pacemaker combination.

A. DOCUMENTATION OF PACEMAKER FUNCTION. Before connection of a new pacemaker to a patient its behavior in vitro, by means of an oscilloscope and a series of load resistances, which can be selected by means of a multipolar switch, is tested. Measurement of the voltage over each resistor will at the same time allow calculation of the current through it. The pulse rate of the pacemaker at each of these resistances should be noted. In some types of pacemakers the rate is dependent on the external load. In case of wire breakage this change in rate may prove to be helpful in diagnosis.

B. DOCUMENTATION OF FUNCTION OF *THE* PACEMAKER-PATIENT COMBINATION. In the postoperative period the course of the wires over their full length and the position of the electrodes are documented for future reference by means of x-ray films. Furthermore, a standard electrocardiogram is obtained for the documentation of the direction and amplitude of the pacemaker artifacts. Proper attention is given to pacemaker rate after implantation, since a subsequent change in rate is an important sign of altered and probably disturbed function.

In patients with disconnectable wires and external pacemakers the threshold and resistance of each wire are measured at least once in the postoperative period by the

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methods discussed below before the patient is discharged from the hospital. It is a considerable advantage of external pacemakers with internal electrodes that electrode resistance and threshold can be regularly checked.

2. *Postfailure analysis.* The clinician should decide whether the cause of failure is localized in the pacemaker proper, in the wire-electrode combination, or in the patient's heart. This decision is facilitated by the following methods.

A. ELECTROCARDIOGRAPHY. The ECG gives four types of information. It will record the rate, direction, and amplitude of the pacemaker artifacts and the form and behavior of the ventricular complexes. The pacemaker rate is compared to the prefailure rate. Any changes in rate should be interpreted in the light of the predetermined dependence of pacemaker rate on load resistance. Wire breakage usually causes higher resistance in the patient circuit because of the smaller surface of the broken wire.

The direction and magnitude of the pacemaker artifacts is carefully compared to the prefailure record. A change in amplitude and direction of the pacemaker artifact is very suggestive of failure in the electrode-wire combination. The mechanism underlying this change is indicated in Fig. 1. The electrodes constitute an electrical dipole the vector of which changes its direction when the wire breaks. A large displacement of an electrode has a similar influence. The electrocardiogram also provides a record of the behavior of the ventricular complexes. Each pacemaker artifact which falls outside the refractory period of spontaneous ventricular activity should be followed by a ventricular complex. Even a single instance of failure of the ventricle to follow the pacemaker should be viewed with the greatest suspicion. Therefore, long strips of record should be obtained and the effect of deep respiration and change of body position noted.

Shortly after wire breakage it is common for the broken ends of the wire to maintain mechanical contact except during special body positions or respiratory maneuvers. The QRS complexes may change their outline because the ventricles change from bipolar to unipolar stimulation (Fig. 2,*A* and *B*).

B. ROENTGENOLOGY. The x-ray film may show a displacement of the wires and electrodes. If superposition of wire shadows is avoided, it may also show the localization of wire breakage. However, it should be stressed that the x-ray films must be of an optimal quality, and that a site of breakage may easily be overlooked unless the entire course of the wires is very patiently scrutinized.

C. CONSTRUCTION OF ISOPOTENTIAL LINES OF THE PACEMAKER ARTIFACT ON THE TRUNK. This procedure may give useful information about the site of wire breakage and the polarity of the broken wire. Exploration with a precordial electrode to find the locus of all points at which the pacemaker artifact is zero establishes the approximate "zero" voltage line. Then isopotential lines can be mapped out by using a bipolar lead, say Lead I. The "right arm" electrode is fixed at an arbitrary site on the trunk and the "left arm" electrode is moved around until once more the locus of all the sites at which the pacemaker artifact shows zero potential with respect to the "right arm" electrode is found. The result of this mapping is a series of more or less concentric curves surrounding sites of maximal positivity and negativity (Fig. 3). Direct-writing electrocardiographs have such a low frequency response as to pass only a small proportion of the voltage of the pacemaker artifact. Therefore, mapping of the isopotential lines is preferably done with the aid of an oscilloscope. It follows

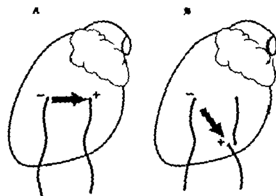


Fig. 1. Schematic diagram of the electrical vector of the pacemaker stimulus before (*A*) and after (*B*) breakage of a pacemaker wire.

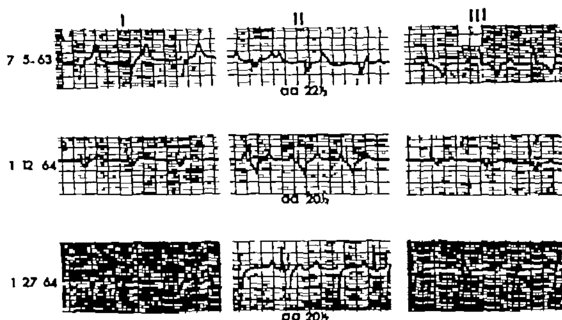


Fig. 2. Electrocardiograms Leads I, II and III from Patient D in the early postoperative period (*A*), after breakage of a wire (*B*), and after grounding of this wire and breakage of the second wire (*C*). Direction and amplitude of the pacemaker artifacts are changed in *B* and *C*. The artifact-artifact (aa) interval is shorter in *B* and *C*.

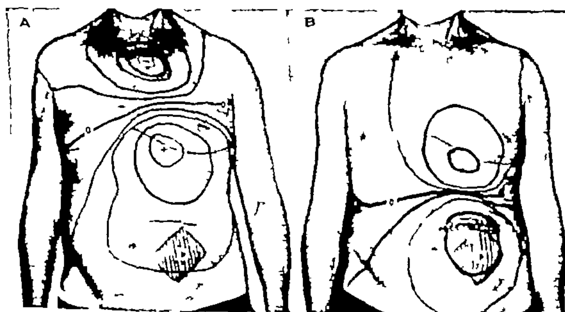


Fig. 3. Mapping of isopotential lines on the trunk of Patient D after the first wire breakage (*A*), and after stripping of the insulation from the positive wire near the pacemaker and breakage of the second wire near its pass through the diaphragm (*B*).

from the concept of the voltage distribution of an electrical dipole in a conducting medium that the zero line should be approximately at right angles to the electrical dipole constituted by the electrodes or wire ends Furthermore some relationship exists between the site and polarity of the voltage maxima on the surface and the spatial site of the poles of the dipole The sites of maximal positive and negative voltage therefore aid in the roentgenologic localization of the wire breakage. If the relative position of the two poles has been identified roentgenologically it is often easy *to tell from the combination with the* pattern of the isopotential lines whether the positive or the negative wire is broken This clinical application of the isopotential lines will be exemplified below

D DETERMINATION OF THE THRESHOLD AND RESISTANCES OF THE WIRE-ELECTRODES. If no fault can be found by this exploration of the electrode wire combination a high stimulation threshold of the myocardium should be excluded as a cause of failure This is done simultaneously with the determination of wire-electrode resistance In patients with implanted pacemakers it is generally necessary to interrupt the continuity of the skin in some way in order to establish an electrical contact with the wire If the pacemaker pocket is opened during this procedure the wires can be separated from the pacemaker and each wire is then individually tested against an indifferent electrode for example a subcutaneous needle

Under aseptic precautions the electrode wire to be tested is connected to an external pacemaker with a continuously adjustable output current This current is measured by means of the voltage appearing over a resistor of known magnitude placed in series with the wire to be tested If this voltage is measured on a dual trace oscilloscope screen simultaneously with the voltage appearing between the electrode wire and the indifferent electrode the total resistance of these electrodes and the patient can be calculated The Medtronics implanted pacemaker[3,4] has a special provision for this measurement The stimulating current is varied in order to find the threshold level for each electrode If during the same session the implanted pacemaker is connected by sterile electrical wires to the same series of load resistors used in preoperative control its response can be measured and compared with preoperative performance

3 *Therapeutic measures* These are determined by the outcome of this analysis A failing pacemaker is exchanged If the threshold is increased the pacemaker can sometimes be replaced by another type if necessary by an external pacemaker with higher output current In the case of wire breakage or electrode displacement of one of a pair of myocardial electrodes, *stimulation can be re-established by unipolar* stimulation using an indifferent electrode For this purpose the broken wire can be used if it is stripped of its insulation This may be done near the pacemaker[8] In those types of pacemakers in which the polarity of the wire cannot be recognized from the outside determination of the polarity through the intact insulation may be accomplished by a pole analyzer using the principle outlined in Fig 4 in which the pacemaker with its wires is schematically represented Current through the wires induces a circular magnetic field in the direction indicated If the current increases

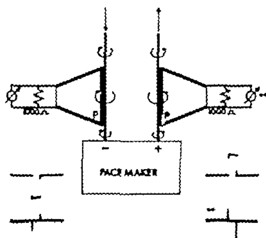


Fig 4 Schematic diagram of the pole analyzer The pacemaker with its positive and negative electrode wires is indicated. Arrow indicates the circular magnetic field surrounding the turns of the coil. Mounted left and right below are oscilloscope pictures from the output signal from the coil when applied to a negative and a positive wire respectively A 1,000-ohm damping resistor is used.

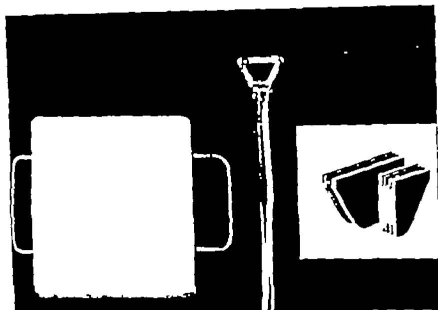


Fig. 5. Practical construction of the pole analyzer. It consists of 520 turns of 0.20-mm. enameled copper wire on a Perspex core. *From left to right:* Aluminum cap for shielding the signal from interference emitted by the pacemaker proper, the pole analyzer applied to an electrode wire, and a diagram of the core construction.

during the rise time of the pacemaker pulse, a voltage spike is induced at the output of a coil held in close approximation to the wire. During the fall time of the pacemaker pulse a second spike is induced with opposite polarity. The practical construction of this simple device is illustrated in Fig. 5.

Confusion is avoided by making the connections in such a way that during the actual preoperative identification a simple rule of thumb can be followed, wherein the first output spike should be positive if the coil is put around the positive wire in such a way that a letter P written on the coil points toward the pacemaker.

Finally, if all wires are broken, or if their threshold has risen beyond the reach of pacemaker power, application of new electrodes, if necessary by a second thoracotomy, may become a necessity.

Case summaries

In *Patient A*, a 74-year-old man with a history of recurrent Stokes-Adams attacks and complete atrioventricular block, a Medtronics double wire-electrode was inserted on Sept. 9, 1961, and connected to an external pacemaker. On Oct. 27, 1961, pacemaker failure occurred. Resistance measurement of the wires showed a normal value for the negative wire (100 ohms) and a high resistance of the positive wire (3,900 ohms). A subcutaneous needle in the abdominal wall was used as an indifferent electrode and unipolar pacing was resumed. On Nov. 20, 1961, it was found that the pacemaker artifacts disappeared from the electrocardiogram on deep inspiration. The resistance of the remaining myocardial electrode-wire was now found to be very high on deep inspiration. It was concluded that this second wire was also broken. A second thoracotomy was performed on Nov. 25, 1961, and four Elema electrodes were implanted and connected to an external pacemaker. This combination functioned well until the patient's death from multiple myeloma on Nov. 25, 1963.

In *Patient B*, a 52-year-old woman, a Medtronics internal pacemaker was implanted elsewhere on Oct. 21, 1962, because of complete atrioventricular block with repeated Stokes-Adams attacks. On March 29, 1963, she was admitted to our department for evaluation of a complaint of vague trembling sensations in the abdominal wall at the pacemaker site. No special attention was paid at that time to the small amplitude of the pacemaker artifacts. On Aug. 2, 1963, the patient died suddenly at home. Postmortem examination revealed an intact wire-electrode system. Examination of the pacemaker, however, showed that the output current had dropped to very low values, and the conclusion was that failure of the pacemaker proper was responsible for the patient's sudden death.

Patient C, 50 years old, suffered from complete atrioventricular block with recurrent Stokes-Adams attacks. On March 23, 1962, four epicardial electrodes were implanted and connected to an Elema external pacemaker. The batteries were changed on July 4, 1962. In January, 1963, the pacemaker rate showed a gradual rise; this was corrected elec-

where by repeated readjustment of the rate controls. Unfortunately too little attention was paid to this phenomenon. On Feb. 2 1963 the patient died suddenly At autopsy the wires were found to be intact, but two of the batteries were exhausted

Patient D a male had a history of repeated Stokes-Adams attacks caused by complete atrioventricular block. On July 5 1963 an Electrodyne TR 14 internal pacemaker was implanted On Jan 10 1964 the patient presented with the complaint that he had observed a rise in his pulse rate from 65 to 70 per minute. This observation was confirmed by comparison with the record made previously (Fig 2,A and B) Besides, it was noted that the direction and amplitude of the pacemaker artifacts had changed. Although every pacemaker artifact was followed by a ventricular complex, a wire breakage was suspected This could not be found on the initial x-ray films

Since the pacemaker had made a quarter turn under the influence of pressure from the waist belt it was suspected that the breakage might be situated near the pacemaker Mapping of the isopotential lines on the trunk (Fig 3 A) showed that the two voltage maxima were far from the pacemaker thus making the assumption of breakage in its neighborhood very unlikely

The zero line and the isopotential lines surrounding the maxima were marked by copper wire and on the x-ray film thus obtained (Fig 6) the breakage point was found to be near the positive maximum. It was clear from this x-ray film that the intact electrode was superior and to the left of the broken wire, and that therefore the broken wire must have a positive polarity

On Jan. 20 1964 both wires were exposed near the pacemaker and the positive wire was identified by means of the pole analyzer (Fig 5). Continuity of the electrical circuit was re-established by "grounding" this wire in the surrounding tissues by removing the insulation over approximately 2 cm after which the pacemaker performed satisfactorily On Jan. 27 1964 there was renewed pacemaker failure. The electrocardiogram showed a 2 1 atrioventricular block and a renewed change in the direction and amplitude of the pacemaker artifacts (Fig. 2,C). The pattern of the isopotential lines was thoroughly changed The center of maximal positivity was seen near the pacemaker where the positive wire had been bared and the maximal negativity was found near the heart (Fig 3,B). The voltage maxima corresponded well with the location of these poles on the x-ray film (Fig 7). On Feb. 5 1964 another thoracotomy was performed and an internal Elema pacemaker was implanted with two functioning and two spare electrodes. Until now the patient is doing well.

Patient E, a 75-year-old man who had had several Stokes-Adams attacks was given an Electrodyne TR 14 internal pacemaker on Oct. 18, 1963 On

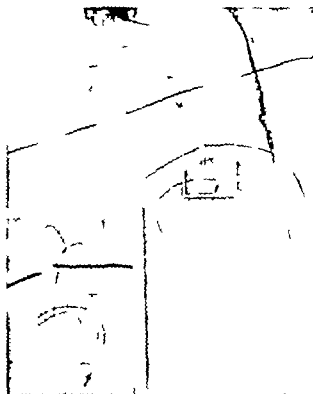


Fig 6 The zero line and some isopotential lines marked by copper wires on the x-ray film of Patient D corresponding to Fig. 3 A *Insert* The site of wire breakage (slightly retouched).

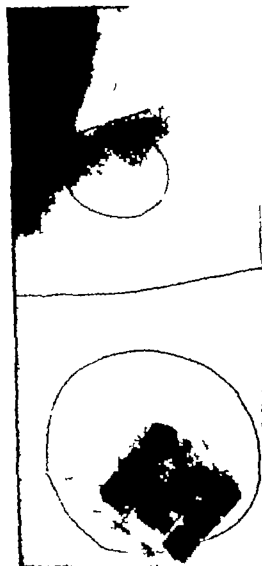


Fig. 7 Zero lines and some isopotential lines marked by copper wires on the x-ray film (Jan. 27 1964) of Patient D corresponding to Fig. 3,B Maximal positivity is found near the pacemaker where the stripped positive wire is imbedded. The area of maximal negativity surrounds the end of the broken negative wire.

Feb. 11 1964 a routine electrocardiogram showed intermittent failure of the pacemaker Amplitude and direction of the pacemaker artifacts were changed and their frequency was slightly higher than that shortly after operation. A chest x-ray film showed that one of the wires was broken near the heart. Comparison of the radiologic findings with the pattern of the isopotential lines led to the conclusion that the polarity of the broken wire was positive. Preparations were made for the "grounding of this broken wire Meanwhile, pacemaker failure had become complete. An x-ray film made shortly before operative exploration showed that the intact wire electrode was displaced and had possibly slipped out of the myocardium Indeed after identification with the pole analyzer and grounding of the positive wire, the heart could no longer be stimulated from the negative electrode. Both wires were withdrawn. One proved to be broken near the electrode the other was intact and must previously have lost contact with the myocardium.

On March 2, 1964 a permanent intracavitary electrode was introduced and connected to an implanted pacemaker

Patient F a 74-year-old man, had also a history of repeated Stokes-Adams attacks and a complete atrioventricular block. On Dec. 14, 1963 an Electrodyne TR 14 pacemaker was implanted. On Jan. 17 1964 the patient observed irregularity of his pulse beat. The pulse rate was 48 per minute. An electrocardiogram showed only occasional stimulation of the ventricles. The pacemaker rate was somewhat higher than shortly after the operation. The amplitude and direction of the pacemaker artifacts were changed. The x-ray films showed breakage of one of the two wires

Comparison of the x-ray findings with results of the mapping of the pacemaker isopotentials on the trunk led to the conclusion that the broken wire had a negative polarity After exposure of the wires the negative wire was identified through the intact insulation by the method described above Its grounding restored pacemaker function.

Two days later the heart rate again fell to 40 per minute The electrocardiogram showed that total failure followed the pacemaker The chest x-ray film showed that the second wire was also broken. An Elema pacemaker with two spare wires was implanted on Jan. 31 1964 The patient is doing well up to the present time.

Discussion

The ease of control of wire integrity in patients with internal electrodes attached to an external pacemaker is exemplified in Patient A, in whom measurement of resistances led to a diagnosis of wire breakage In other similarly treated patients not included in this series, high thresholds were found with normal resistances, probably pointing to the development of connective tissue around the electrodes. Connecting the pacemaker to a spare electrode forestalled failure.

Failure to pay attention to the small voltage of the pacemaker artifacts and to the change in pacemaker rate, respectively may have contributed substantially to the death of our Patients B and C The case summaries of Patients D E and F reflect our increasing awareness of the significance of changes in rate in direction, and amplitude of the pacemaker artifacts

and the use of the combined results of x-ray examination and mapping of the isopotential lines of the pacemaker artifact on the trunk of the patient The broken wire was operatively exposed and correctly identified by the pole analyzer and pacing was restored after grounding of the broken wire in Patients D and F Therapeutic success was of disappointingly short duration because of breakage of the second wire shortly after the first No explanation is offered for the remarkable similarity in lifespan of a pair of implanted wires in these cases but it is assumed that in other cases the second wire may remain intact for considerably longer periods It is hoped that in such cases the methods outlined above may add to the lifespan both of the pacemaker system and the patient.

Summary

Some aids to electrical diagnosis of pacemaker failure are described These consist of careful preoperative appraisal of pacemaker function and immediate postoperative electrocardiographic recording of rate and form of the pacemaker artifacts and of the postfailure comparison of these same features Mapping the isopotential lines of the pacemaker artifacts on the patient's trunk, in combination with x ray analysis aids in the localization of wire breakage and in the determination of the polarity of the broken wire Some therapeutic implications of this analysis are exemplified and discussed

We wish to express our gratitude to Prof Dr D Durrer for his help and support to Prof Dr L. H van der Tweel for his invaluable help in the early phases of our pacemaker troubles, and to Prof Dr B G Ziedses des Plantes and his staff for their contribution to Figs. 6 and 7

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Blood coagulation studies in children with congenital heart disease

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Coagulation defects in infants and children with congenital heart disease is a subject about which little can be found in the literature. There are studies dealing with coagulation defects associated with cyanotic congenital heart disease,[1-4] but none could be found dealing specifically with coagulation defects associated with acyanotic congenital heart disease. None of the studies of coagulation defects in children with congenital heart disease included controls by which a comparison could be made.

The present study was undertaken to see whether any relationship could be shown between coagulation defects and congenital heart disease, with special attention being paid to the acyanotic group.

Methods

In our study, five tests were performed and the findings therefrom were designated as a coagulogram. These tests served as a basis for the determination of coagulation defects.

1. *Platelet counts* were made by the modified Reese-Ecker method.[5] Normal counts range between 200,000 and 400,000 per cubic millimeter.

2. *Clot retraction* was done by the oil suspension method of Budtz-Olsen,[6] the normal being a contraction of 30 per cent or more at 20 to 25°C. in 24 hours.

3. *Clotting time* was measured by the modified Lee-White method,[7] the normal range being from 9 to 18 minutes at 25°C.

4. *Prothrombin* consumption tests were performed by a 1-stage method, the normal time being 30 seconds or more in 1 hour.

5. *One-stage prothrombin* time determinations were made,[8] the normal range being 70 per cent or more of the control value (14.2-14.8 seconds).

6. Testing for Factor VII[9] and Factor X[10] deficiency was also done.

Case material

The cardiac patients who were evaluated underwent cardiac catheterizations, angiocardiography, or operation in order to ensure diagnostic accuracy. On this basis, as well as by clinical history and arterial oxygen saturation studies, the pa-

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Table I. Group I. Acyanotic congenital heart disease (subdivided according to specific defect)

Case number	Clot time	1st S.P. (%)	C.R. (%)	P.C.	Plat.	Other	Operation	P.O. blood (c.c.)	P.H.
Ventricular Septal Defects									
1	10	45	0	73	165	X			
2	8	100	40	37	279				
3	13	70	0	26	354				
4	27	14	0	32	170				
5	6	100	30	42	71				
6	14	45	37	23	160	VII			
7	16.5	80	30	24.5	179				
8	8	100	50	32	265				
9	15	90	23	45	185	VII			
10	13	100	42	23	292				
11	12	80	35	60+	190				
12	1	100	35	36	201				
13	11	70	35	31	234				
14	10	100	6	70	237				
15	6	95	60	50	210				
16	12	45	27	42	188	VII			
17	14	95	6	53	193		x	250	
18	8	100	30	65	185		x	250	
19	8	60	55	26	197	VII	x	300	
20	11	100	42	48	312		x		
Patent Ductus Arteriosus									
1	12	60	35	43	163	VII	x		
2	26.5	55	28	36.5	231		x		x
3	6.5	90	37	32	124		x		
4	12	55	28	33	257	VII	x		
5	7	75	50	48	240		x		
6	9	85	29	26	432		x		
7	12	90	0	29	233		x		
8	6	85	—	50	117		x		
9	8	55	0	26	161	VII	x		
10	12.5	73		80	208		x		
11	11	100	50	53	240		x		
12	7	85	48	45	292		x		
13	9	50	30	31.5	191	X	x		
14	6	85	9	39	430		x		
15	18	100	32	41	720		x		
16	6	100	52	32	113		x		
Atrial Septal Defects									
1	7	55	23	65	240	VII	x	550	
2	7	55	45	60+	268	VII	x	1,000	
3	7	90	3	23	61		x	100	
4	9	80	10	35	132		x		
5	9	35	41	27	48	Prothrombin deficiency	x		
6.	18	63	31	16	165		x	100	
7	10	65	46	45	126		x	400	
8	13	45	36	27	325	VII	x	500	
9	18	55	45	35	292		x	1,300	
10.	13	100	40	36	228	VII	x	830	
11	7.5	70	0	60+	326				
12	8	90	3	58	297				
13	12	40	0	60+	180	X			
14	8	80	28	43	422				

1st S.P.: First-stage prothrombin. C.R.: Clot retraction. P.C.: Prothrombin consumption. Plat: Platelets (thousands per cubic millimeter). Other: Other factor deficiency. P.O. Blood: Postoperative blood. P.H.: Past history of bleeding.

Table I. Group I. Acyanotic congenital heart disease (subdivided according to specific defect)—Cont'd

Case number	Clot time	1st S.P (%)	C.R. (%)	P C	Plat	Other	Operation	P.O. blood (c c)	P H
Pulmonary Stenosis									
1	11.5	80	49	60+	240		x		
2.	14	80	17	59	39		x		
3	10	95	31	37	350		x		
4	10.5	100	30	33	177		x		
5	8	35	8	36	235	VII	x		
6.	10	95	29	35	211		x		
7	6	65	40	35	109				
8	15	100	9	40	252				
9	12	100	41	34.5	210				
10	14	35	43	42	220				
Pulmonary Stenosis with Ventricular Septal Defect									
1	26	75	42	25	308		x	250	
2	3	35	—	31	86		x		
3	8	65	9	90	57	X			
4.	15	70	0	31	230				
5	16	85	40	30	219		x	1 000	
Miscellaneous									
1	17	50	—	26	206				
2.	12	35	9	47	283				

tients were divided into three main groups.

Group I. Acyanotic congenital heart disease. This group included patients with an arterial oxygen saturation above 91 per cent and was subdivided according to specific defect. (See Table I for the results.) Of the 3 patients with pulmonary stenosis and associated ventricular septal defect who underwent operation, 2 died one with hemorrhage and one with cardiac arrest.

Group II. Cyanotic congenital heart disease. This group included those patients with an arterial oxygen saturation of less than 80 per cent and was also subdivided. (See Table II for the results.) Of 10 patients with tetralogy of Fallot who underwent operation, 2 died one of hemorrhage and one of anoxia.

Group III. Slight cyanosis. This group consisted of patients who had arterial oxygen saturation levels between 80 and 91 per cent and/or intermittent cyanosis clinically. (See Table III for the results.)

Group IV. Controls. This group consisted of patients selected at random from our outpatient clinic population. The requirements for this group were (1) that they be within the age range of 3 months to 15 years, and (2) that they have no known blood dyscrasia or any heart, liver or other disease which might affect blood coagulation. Only 7 patients of this group had completely *normal coagulograms.* (See Table IV for the results.)

Discussion

By extension of the median test, statistically significant correlations were found between cyanotic congenital heart disease with both thrombocytopenia and oil clot retraction ($p < .01$) and acyanotic heart disease with oil clot retraction only ($p < .05$).

The oil clot retraction is the least sensitive and least reliable of the five coagulation tests. The significant correlation between cyanotic heart disease and thrombocytopenia has previously been reported.[1-4] We do not believe that there is a significant relationship between coagulation problems

Table II Group II Cyanotic congenital heart disease (subdivided according to specific defect)

Case number	Clot time	1st S P ( )	C R (	P C	Plat.	Other	Operation	P.O blood ( )	P.H
Tetralogy of Fallot									
1	14	40	0	—	76		x		
2	10	75	1[illegible]	60	171		x		
3	11	0	25	46	150		x		
4	7	90	3	60+	116		x		
5	9	90	70	39	292		x		
6	1	80	23	50	200		x		
	10	75	—	3[illegible]	319		x		
8	9	100	17	58	216		x	250	
9	5	100	20	—	58				
1[illegible]	1	60	4	38	145	VII			
11	8	100	35	60+	200				
1	13	85	14	41	146				
13	9	5	37	31	325				
Others									
1	10	5	38	60+	145		x		
	17 5	95	18	28	150		x		
3	1	55	50	60	291	X	x		
4	5	100	55	19	275		x		
5	21	55	3	60+	84	VII			
6	13	50	37	41	251	VII			
	13	60	23	31	35[illegible]				
8	9	100	0	31	147				
9	3	100	—	29	161				
10	16	85	—	—	53				

For key to abbreviations see footnotes to Table I

Table III Group III Slight cyanosis

Case number	Clot time	1st S P (	C R ( )	P C	Plat	Other	Operation	P.O blood ( )	P.H
1	10	45	33	60+	279	X			
	9	45	0	45	222	X			
3	[illegible]	0	40	42	304				
4	9	90	19	5	307				
5	9	60	2[illegible]	[illegible]8	190	X			
6	8 5	100	44	29	147				
	12	80	17	4[illegible]	192				
8	10 5	65	42	3[illegible]	241	VII			x
9	13	25	43	28	[illegible]38	X			
10	9	35	20	33	248	X			
11		100	15	65	240				
1[illegible]	13	100	50	75	208				
13		35	0	27	193	VII	x	100	x
14	10	100	38	60+	326		x		
15	10 5	55	4	55	410	VII	x		
16	12	50	30	60+	379	X	x		
17	4	30	33	34	10[illegible]	VII	x		
18	1	45	31	30	210	VII	x	1 500	
19	13	60	0	40	[illegible]94	X	x		
20	11	60	33	2	281		x		x

For key to abbreviations see footnotes to Table I

Table IV Group II Controls

Case number	Clot time	Id S.P (%)	C.R. (%)	P C	Plat.	Other	Operation	P.H
1	12	35	43	55	348	VII		
2	12	40	33	60+	318	X		
3	13	100	22	49	390			
4	11.5	100	40	51	284			
5	12	70	64	38	312			
6	18	50	44	36	256	X		
7	14	40	63	44	203	X		
8	10	55	34	47	263	VII		
9	13	35	58	50	241	VII		
10	13	75	24	41	230			
11	14.5	20	30	41	221	VII		
12	10	70	44	60	334			
13	11	25	47	40	255	X		
14	10.5	35	31	60+	298	X		
15	11	40	42	55	421	VII		
16	18	45	40	37	218	VII		
17	12	100	43	39	183			
18	12	90	34	37	198			
19	8	93	37	23	197			
20	14	45	28	40	380	X		
21	9	43	28	40	204	X		
22	16	100	40	51	193			
23	3	90	40	21	344			
24	11	85	28	17	270			
25	10	63	26	60	210			
26	14	60	41	60+	363	X		
27	13.5	100	32	60+	308			
28	8	100	40	56	186			
29	10	70	38	43	364			
30	6	65	34	44	308	X		
31	9	60	42	46	243			
32	14	70	18	41	228			
33	14	100	37	60+	208			
34	12	100	35	40	197			
35	11.5	100	37	34	244			
36	6.5	100	34	60+	423			
37	18	50	46	48	333	X		
38	10	85	46	60+	131			

For key to abbreviations see footnotes to Table I

and acyanotic congenital heart disease in children

Although other investigators have shown defects in coagulation in children with cyanotic congenital heart disease no studies were found in the literature in which comparison was made with a control group. Superficially this would appear to be unnecessary since there are established standard values. However in our study most of the controls had some abnormality which eliminated the apparent significance of most of the abnormal coagulation findings in the group with congenital heart disease It is our opinion that this is most significant Also although abnormal findings with the coagulation tests were frequent in the patients with heart disease, bleeding problems with or without surgery were rare

Thus, although preoperative coagulation studies in children with congenital heart defects may be advisable the results should be interpreted cautiously

Lastly we can only speculate with regard to the high incidence of abnormal coagulation findings in our control patients

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Postinfarction ventricular aneurysm

A clinicomorphologic and electrocardiographic study of 80 cases

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The results of different studies of the clinical and morphologic features of ventricular aneurysms occurring after myocardial infarction have led to different conclusions in regard to their frequency,[1-10] the factors contributing to their development,[1,4,11,14] and their prognosis.[7,11,14-18] Therefore, we reviewed instances of this condition observed at necropsy at the Mayo Clinic in recent years. In addition to analyzing and correlating clinical and morphologic aspects of postinfarction ventricular aneurysms, we searched for factors that might be related to prevention, diagnosis, and prognosis of this complication of myocardial necrosis.

Materials and methods

In this study, the definition of ventricular aneurysm proposed by Edwards[19] was followed. Thus, a ventricular aneurysm was defined as a protrusion of a localized portion of the external aspect of the ventricle accompanied by a corresponding protrusion of the ventricular cavity. This definition eliminated instances of healed myocardial infarction in which a scar resulted in a thinned area of the ventricular wall and instances of localized bulges of the ventricular cavity into a scar without any change in the external contour of the ventricle.

The necropsy files of the Mayo Clinic for the years 1952 through 1963 were reviewed for instances of ventricular aneurysm that fit this definition. The gross morphologic and histologic features of the cases were studied, and the clinical histories, the roentgenograms, and the electrocardiograms were reviewed.

Results

In the 12 year period studied, 87 instances of ventricular aneurysm in 80 hearts were found. The 80 hearts were 3.5 per cent of the 2,293 hearts with old or recent myocardial infarction observed during this time, in which 10,800 necropsies had been performed.

Morphologic features. Most of the aneurysms were of the diffuse type, although occasional instances of ventricular aneurysm with a short, broad neck communicating with the ventricular cavity were observed. The thickness of the wall of the aneurysm ranged from 1 to 6 mm. Histologically, the aneurysmal wall was composed of hyalinized fibrous tissue together

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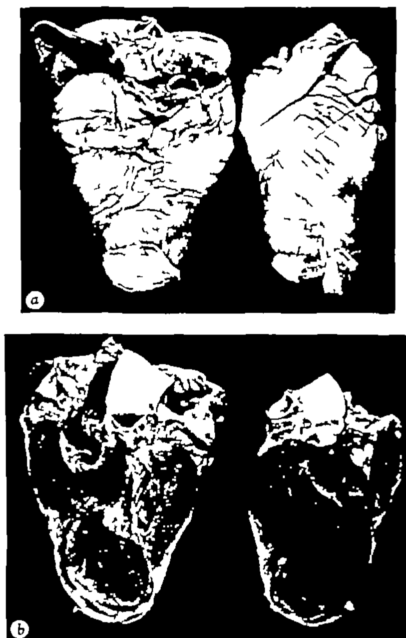


Fig. 1. *a*, Typical anterior apical ventricular aneurysm with external deformity and adherent pericardium. *b*, Hemisection of heart shown in *a*. Ventricular aneurysm involves the entire apex with mural thrombus.

with residual muscle bundles in most cases; there were focal areas of calcification in a few cases. All 82 aneurysms were in the left ventricle. In 63 (79 per cent) of the hearts the aneurysms were located in the anterior half of the left ventricle including 49 in the apex (Fig. 1). In the remainder the aneurysms were in the posterior part of the heart in 15 (19 per cent); 3 were apical and 12 were posterior basal (Fig. 2). The other 2 hearts each had two aneurysms: an anteroapical and a posterolateral aneurysm in one, and an anterior and a posterolateral aneurysm in the other. The aneurysms ranged from 2 by 2 cm. to 15 by 14 cm., with an average of 5.6 by 5.2 cm., but the size was not related to the location.

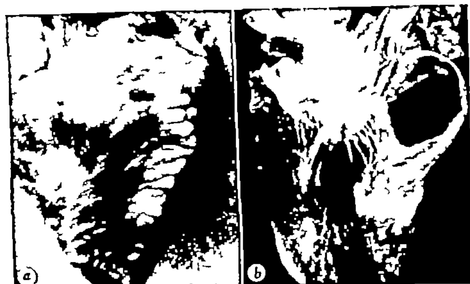


Fig. 2. a, Typical posterior basal ventricular aneurysm. b Hemisection of heart shown in a demonstrates a large saccular posterior basal aneurysm with mural thrombus.

Severe coronary artery atherosclerosis was present in all cases. In most instances the most severe degree of narrowing or occlusion of the coronary arteries could not be specifically correlated with the location of the aneurysm because severe or occlusive lesions of equal degree were present in more than one major coronary artery Among the hearts with anterior aneurysms, occlusive lesions of the left coronary artery or its major branches were present in 33 occlusive lesions of the right coronary artery were present in 1 and occlusive lesions of both arteries were present in 18 Similarly of the hearts with posterior aneurysms, 5 had occlusive lesions of the left coronary system 2 had them in the right, and 6 had them in both. Occlusive lesions were found in both coronary arteries in one of the two hearts with multiple aneurysms, and only in the right coronary artery in the other Although complete occlusion of the coronary arteries was not found in the 13 other cases, more than 75 per cent of the lumen of one or more coronary arteries was obliterated in 11

Scarring of a papillary muscle existed in 26 (33 per cent) of the hearts, but in no instance was the base of the papillary muscle incorporated into the aneurysm Calcification was present in 9 hearts In 5 of these it was grossly visible, whereas in the 4 others it was found by histologic examination.

On the basis that increased heart weight existed only when the heart weighed at least 100 grams more than the expected normal an increased heart weight was present in 66 cases (83 per cent) Twenty two of these hearts were from patients who had been known to be hypertensive, and 34 were from patients who had had congestive heart failure.

Pericardial thickening or adhesions overlying the aneurysm were observed in 49 hearts (61 per cent) Hemopericardium was present in 2, and rupture of a posterior basal aneurysm had occurred in one of these.

Mural thrombi within the aneurysm were found in 52 hearts (65 per cent) In 30 of the 80 cases systemic arterial occlusion—presumed to be of embolic origin—had occurred with infarction of the tissue supplied by the affected vessel Nineteen (63 per cent) of the 30 had mural thrombi the thromboemboli were responsible for death in 7 patients and contributed to the fatal outcome in 3 others.

Clinical features Sixty five (81 per cent) of the patients were men whose ages ranged from 43 to 96 years, with a mean of 67 years. The 15 women ranged in age fr

Table I. Cause of death in 80 patients with postinfarction ventricular aneurysm

I Cardiac decompensation				
A Direct cause of death			46	(57.5%)
Patients with history or presence of hypertension		11		
B Contributory cause of death			15	(17.5%)
Patients with history or presence of hypertension		5		
	Total		61	(75%)
II Coronary artery insufficiency				
A Acute myocardial infarction				
1 Direct cause of death			9	(11%)
2 Contributory cause of death			25	(31%)
B Acute coronary insufficiency without myocardial infarction			7	(9%)
C Cardiac rupture			1	
	Total		42	(53%)
III Thromboemboli				
A Direct cause of death			7	(9%)
B Contributory cause of death			3	(4%)
	Total		10	(13%)
IV Surgical treatment				
Ventricular fibrillation (5 days after resection of ventricular aneurysm)			1	
V Miscellaneous (unrelated to cardiac status)				
A. Metastatic disease		5		
Cancer of stomach	3			
Cancer of colon	1			
Cancer of lung	1			
B Uremia secondary to obstructive uropathy		1		
C Pulmonary embolus (8 days postgastrectomy)		1		
D Pneumonia		1		
E Suicide (hanging)		1		
	Total		9	(11%)

57 to 87 years with a mean of 71 years. Hypertension defined as a systolic blood pressure greater than 150 mm. Hg and a diastolic blood pressure greater than 90 mm. Hg had been recorded in 23 cases. The major symptoms and signs were referable to coronary artery disease. Fifteen patients had had no symptoms of cardiac disease. The causes of death of the 80 patients are summarized in Table I.

In 48 patients it was possible to estimate the period between the antecedent acute myocardial infarction which was presumed to be the basis for the aneurysm and the time of death although a history of a myocardial infarction at some previous time was obtained in 58 cases. Of these 48 patients, 20 died within 1 year, 9 within 1 to 3 years, 6 within 3 to 5 years, 9 within 5 to 10 years, and 4 within 10 to 15 years.

Information concerning the treatment of the myocardial infarction presumed to be responsible for the ventricular aneurysm was available in 62 cases. Thirty-four of these 62 patients had had 3 or more weeks of bed rest. 27 had had less than 3 weeks of bed rest, and 1 patient died in less than 3 weeks while at bed rest. Anticoagulants had been given to 22 patients (the exact duration of this treatment could not be ascertained) and of these, at necropsy 8 were found to have had thromboembolic phenomena: more than half had mural thrombi within the aneurysm and 4 had both mural thrombi and thromboembolic disease.

Posteroanterior thoracic roentgenograms, as routinely interpreted, were considered to demonstrate cardiac enlargement in 36 patients, and a ventricular aneurysm in only 1 patient. In the other cases the roentgenograms either were reported to be negative or were not available for review.

The clinical diagnosis of postinfarction ventricular aneurysm was made in 13 of the 80 patients (16 per cent). It was based on roentgenographic and electrocardiographic data in each instance.

Electrocardiographic findings. Electrocar-

diograms were available for review in 50 of the cases of anterior aneurysm, 13 of the cases of posterior aneurysm and in the 1 case of both an anterior and a posterolateral aneurysm.

Among the 50 patients with an anterior aneurysm 37 had the pattern of an anterior myocardial infarction, 1 had the pattern of a diaphragmatic infarction and 6 had a pattern that suggested combined anterior and diaphragmatic infarction. Twelve of these 50 had conduction disturbances: 6 instances of intraventricular block, 2 of right bundle branch block, and 4 of left bundle branch block. In 9 of the 50 patients, arrhythmias had been recorded: 5 instances of atrial fibrillation, 2 of ventricular tachycardia, 1 of atrial tachycardia and 1 of frequent ventricular extrasystoles. In 33 of these 50 patients an electrocardiogram had been taken more than 30 days after the onset of the acute infarction and at a time when there was no clinical evidence of myocardial ischemia; in 26 of the 33 a pattern of persistent S-T segment elevation in the precordial leads was observed.

Among the 13 patients with a posterior aneurysm, a pattern of anteroseptal infarction was present in 2, diaphragmatic infarction in 4 and combined patterns in 4. 1 patient had an intraventricular block, and 3 had recorded arrhythmias which consisted of atrial fibrillation in 1, atrial and ventricular tachycardias in 1 and ventricular tachycardia in 1. Persistent S-T segment elevation in standard Leads II, III and aVF or S-T depression in the precordial leads or both were observed in 4 of 8 patients in whom a recording was obtained at least 30 days after the onset of infarction.

S-T segment changes of these types were not present in the electrocardiogram of the patient with two aneurysms.

Comment

The differences in incidence of ventricular aneurysms reported[1-11] as occurring after myocardial infarction are partly dependent on differences in definition of this condition. Using the criteria of Edwards[30] we observed that ventricular aneurysms developed in 3.5 per cent of patients with healed myocardial infarction, as compared to an average incidence of 10 per cent in the studies cited. Males predominated in this study by a ratio of 4:1, in contrast to the male-to-female ratio of 2.5:1 observed among patients with myocardial infarction.

The ventricular aneurysms in this series did not differ significantly from those of previously reported cases, in regard to location, size, occurrence of mural thrombi, presence of calcification, incidence of thromboembolic complications, frequency of rupture and associated cardiac conditions.[illegible] In agreement with previous reports,[illegible] our findings in regard to heart weight suggested that hypertrophy may result from the presence of the aneurysm alone. Pericardial changes appeared to be the consequence of the previous infarction rather than a result of the aneurysm itself. The results of this study supported the view that thromboembolic complications were a more frequent hazard with a ventricular aneurysm[illegible] than with a healed myocardial infarction without aneurysm.[illegible]

In this study, clinical signs and symptoms related to the presence of the aneurysm were infrequently recorded. The presence of hypertension, or a history of it, in 29 per cent of the patients did not permit any conclusion in regard to the positive[illegible] or the negative[illegible] role of hypertension in the development of a postinfarction ventricular aneurysm. Cardiac decompensation was a frequent problem in the cases reported herein. We suggest that the enlargement of the left ventricle, with resultant increase in the radius of curvature and hence increased myocardial tension according to the law of Laplace, results in decreased myocardial efficiency, which sets the stage for decompensation. Although inadequate bed rest after myocardial infarction has been suggested to be a factor in the development of ventricular aneurysms,[illegible] this factor could not be considered to be definitely significant in our series, because more than one half of these patients had had 3 or more weeks of bed rest. Although definite conclusions could not be drawn, anticoagulant therapy seemed to offer only limited protection against the development of [illegible]

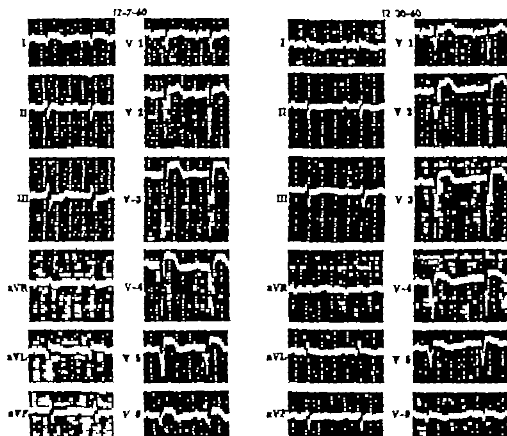


Fig 3 Electrocardiogram with typical S-T changes seen with anterior aneurysm. The tracing at left (*12-7-60*) was taken during an episode of acute myocardial infarction. The tracing at right (*12-30-60*) taken 3 weeks later shows persistence of S-T segment elevation in leads overlying the aneurysm

rysm and against the occurrence of thromboemboli

In general routine thoracic roentgenograms rarely lead to the diagnosis of ventricular aneurysm However the value of more complex radiologic methods (cardiac fluoroscopy electrokymography and angiocardiography) in this regard has long been known That electrocardiograms could be of value in the diagnosis has been indicated previously[1,4,5-21] and was supported by our finding of persistent S-T segment elevation in leads over the lesion in 79 per cent of anteriorly situated aneurysms (Fig 3) and 50 per cent of posteriorly situated aneurysms.

Since the 5 year survival rate of patients with postinfarction aneurysms was 27 per cent, as contrasted to a 5-year survival rate of 74 per cent[9] for patients surviving the acute stage of myocardial infarction we concluded that the prognosis for life was worsened by the presence of the aneurysm This conclusion was similar to that reached by some[7,12,42,44] and opposite to that of other workers.[13,14,18,42-44]

Summary and conclusions

Aneurysm of the left ventricle occurred in 80 patients (3 5 per cent) among 2 293 who had recent or old myocardial infarction in a series of 10,800 consecutive necropsies from 1952 through 1963 Males predominated by a ratio of 4 1 The aneurysm was situated in the anterior portion of the left ventricle in 63 hearts and in the posterior portion in 15 and two discrete aneurysms were present in 2 Mural thrombi occurred in 65 per cent of the aneurysms, and systemic thromboembolism occurred in 38 per cent of the cases. Rupture of the aneurysm occurred in one case. The most common causes of death were congestive heart failure (75 per cent) coronary artery

insufficiency with or without myocardial infarction (53 per cent) and thromboembolic disease (13 per cent).

No specific symptoms or physical signs of the aneurysm had been recorded in any patient. More than half of the patients had had 3 or more weeks of bed rest as part of the treatment for the antecedent myocardial infarction. In the small number of cases in which it could be evaluated anticoagulant therapy did not uniformly prevent the development of mural thrombi within the aneurysm or the occurrence of thromboemboli. Although no pathognomonic electrocardiographic pattern could be found persistent S-T segment abnormalities were observed frequently. The duration of life from the time of the myocardial infarction presumed to be the basis for the aneurysm was less than 3 years in 60 per cent and less than 5 years in 73 per cent of the cases.

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Experimental and laboratory reports

Incoordination of the cardiac contraction, as judged by the force ballistocardiogram and the carotid pulse derivative

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Increasing interest in the clinical significance of incoordination of the cardiac contraction[1] has led us to continue clinical studies by taking simultaneous records of ULF force Bcgs and the first time derivative of the carotid pulse. Such a study has the aim of improving our ability both to detect the presence of cardiac incoordination and to distinguish one type from another for an incoordination due to asynchronism in performance of the two sides of the heart may well have a clinical significance different from that of an incoordination due to abnormality of the contraction of one ventricle.

Certain similarities between the contours of pulse and force Bcg have been recognized for some time. That force Bcg amplitude was related to the slope of the ascending pulse wave front rather than to pulse amplitude was noted in a case of irregular rhythm about 20 years ago,[2] an observation which plainly suggested that the force Bcg was related to the pulse derivative.

When systole was simulated in cadavers both pulse contour and force Bcg proved to be related, through the calculus, to the curve of cardiac output at each instant of ejection the pulse being an adjusted first derivative of that curve,[3] whereas the force Bcg more nearly resembled the second or third derivative.[4] However it was always obvious that both records were imperfect representations of the derivatives of the cardiac ejection curve, the force Bcg being greatly changed by the reversal of blood direction in the arches the central pulse requiring a mathematical adjustment described [3] and the peripheral pulse being further altered by change of contour and loss of high-frequency information as the wave descends the arteries.

Other authors have also noted interesting relationships in the records they secured Burch[5] observed resemblances between Bcgs and high derivatives of volume records secured by a finger plethysmograph Reeves and associates[6] found that the contour of a calculated second derivative of a carotid pulse record resembled that of a normal force Bcg

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Comparing the ULF force Bcg with the *brachial* pulse derivative Starr and Ogawa[7] found a marked similarity between the contours in certain parts of the two records in healthy persons. In many patients the contours of both records were distorted but they closely resembled one another only rarely. Obviously the failure of these abnormal records to look more alike might have been due to many causes, one of which was the distortion of the pulse as it moved down the vessel to the transducer on the brachial artery. This conception could be tested and in this study to secure a pulse nearer to its source in the heart the *carotid* pulse has been recorded.

It was at once apparent that the first derivative of the carotid pulse resembled the ULF force Bcg much more closely than did that of the brachial pulse and with this improvement in technique has come we believe increased ability to make an exact analysis of the cardiodynamics of any patient by taking both records simultaneously.

Methods and subjects

To secure carotid pulse records a Brecht and Bouche capacitance transducer[4] was enclosed in a small iron framework which when bound to the neck held the transducer head away from the skin. A short iron rod screwed into the head projected 2.5 cm. beyond the framework its tip making contact with the skin over the artery. The differentiating circuit has been described.[7] Used with a Sanborn Twin Viso recorder the frequency characteristics of the system were satisfactory for our purpose.

The healthy subjects were drawn from medical students and the hospital staff and the patients were from the medical wards of the University Hospital. Only ambulatory patients were studied. In all 100 persons were tested.

The subjects lay for 15 minutes on a ULF force Bcg[8] before being tested. During this rest period the Bcg was calibrated.[9] With the head turned about 30 degrees away from the carotid artery to be used the point of maximum pulsation was identified by palpation the tip of the transducer rod was applied to it and the transducer bound down by a strap around the neck. Several locations were tried and that giving the most normal record was selected. We then took simultaneous records of conventional pulse and pulse derivative pulse and Bcg and pulse derivative and Bcg. Blood pressure was taken by the auscultatory method during or at the end of the test.

In addition to the records taken at rest records were secured before, during and after the action of 0.6 mg. of nitroglycerine placed under the tongue in 16 subjects chiefly elderly persons or those with obvious cardiac abnormalities.

The base line and calibration of the carotid pulse derivative can be determined in the same manner as were those of the brachial pulse derivative by Starr and Ogawa.[14] Simultaneous records of derivative and conventional pulse are taken and from auscultatory blood pressures taken before or after the test systolic and diastolic pressures can be assigned to the conventional pulse and a scale of its pressure values so determined. A line is now drawn tangent to the conventional pulse at its point of steepest ascent this point may be identified by its alignment with the peak of the derivative taken simultaneously. From the tangent of the angle of this line with the horizontal the peak value of the derivative can be calculated as described by Starr and Ogawa[14] who give an example. Since the calibration of the derivative is linear this point and the base line determine it.

Results

The normal carotid pulse derivative secured in healthy young adults was so similar to the normal brachial pulse derivative described in detail by Starr and Ogawa[14] that a detailed description and measurements will not be given here. As will be seen in Figs. 1 and 3 the chief features consist of a main wave (ABC) whose straight ascending limb (AB) starts at the onset of ejection and rises rapidly to a single tip. The smooth descending limb (BC) which tends to be concave is not so steep as the ascending one. This main wave either directly or after a brief interval during which the record runs nearly parallel to the base line is followed by a sharp deflection (CDE) opposite in

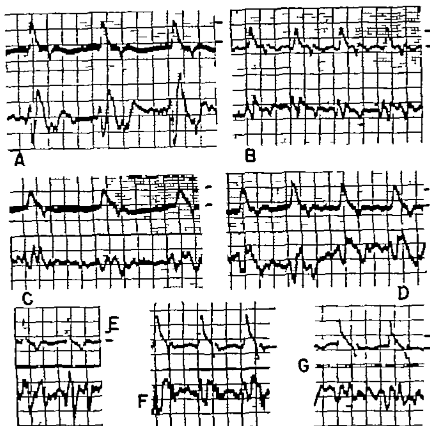


Fig. 1. Comparison between the carotid pulse derivative (*above*) and the ULF force ballistocardiogram (*below*) when the pulse derivative is normal in contour. The Bcgs were standardized so that a force of 280 grams deflected the record 15 mm. The standardization of the pulse derivative is placed on each record, the base line and 500 mm. Hg/sec. being indicated. *A*. H.S., age 23, B.P. 120/70 mm. Hg, a normal young adult. Both records are normal. The similarity of contour is especially noteworthy in the last complex shown. *B*. A.W., age 37, B.P. 120/80 mm. Hg, myocardial infarct 6 months before test. Bcg amplitude poor for his age. Smaller complexes could not be passed as normal. Note striking similarity of larger complexes with pulse derivative. *C*. T.S., age 49, B.P. 150/100 mm. Hg, hypertension. ECG showed left ventricular strain. Note that normal pulse derivative contrasts with deeply divided Bcg J wave. *D*. L.B., age 17, B.P. 110/65 mm. Hg, rheumatic heart disease. Note slight notching of J despite normal pulse derivative. *E*. D.W., age 59, B.P. 130/60 mm. Hg, emphysema. Formerly congestive failure. Note that narrow pulse derivative deflection coincides with abnormally narrow J wave, but the J wave is also deeply divided by an abnormal footward force giving the deepest footward deflection on the record. Nothing in the pulse derivative corresponds to this footward wave, so that its origin is attributed to forces of the right ventricle. *F*. W.L., age 67, B.P. 115/79 mm. Hg, after left pulmonectomy for carcinoma. ECG showed right bundle branch block. Note distortion of the I and J waves not shown in pulse derivative. *G*. J.P., age 72, B.P. 110/60 mm. Hg, right pleural effusion. ECG showed flat T waves in all leads. Note grossly abnormal contour of Bcg in presence of normal pulse derivative.

sign to the main wave and of much smaller magnitude. This smaller wave occurs at the time of the incisura of the conventional pulse record, and so after allowing for the pulse transit time, marks the end of ejection. Still smaller waves, seen occasionally in diastole and just before ejection, are not a constant feature of these records.

Abnormal records contain notches or shoulders on either limb of the main wave, doubled main waves, main waves with flat tops, rounded take-off angles, and other gross distortions of the normal architecture. Abnormal records, such as those given in Figs. 2 and 3, are encountered in patients suffering from many types of heart disease and in elderly persons. Our chief interest was in comparing such abnormalities with those of the force Bcg.

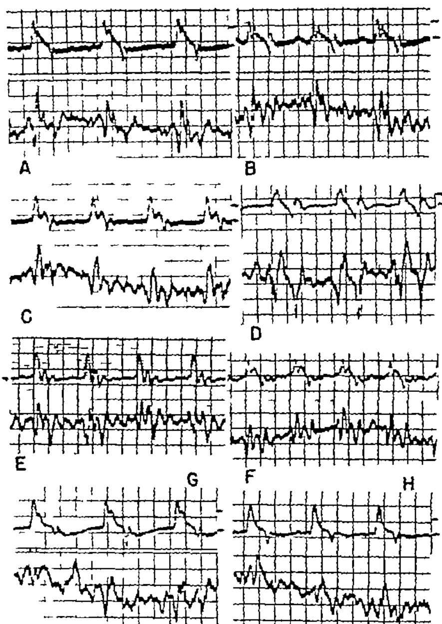


Fig. 2. Comparison between the carotid pulse derivative (above) and the U.L.F. force Bcg (below), when the pulse derivative is abnormal in contour. Standardizations as in Fig. 1. A, S.T., age 60, B.P. 145/90 mm. Hg. Note that notch on descending limb of pulse derivative is duplicated by notch in Bcg. B, H.E., age 42, B.P. 140/80 mm. Hg, weight 219 pounds, diabetes mellitus, pyelonephritis. Note that deep notching of pulse derivative corresponds to notching on Bcg J wave. C, R.D., age 64, B.P. 150/95 mm. Hg, diabetes mellitus, hypertensive cardiovascular disease. Note that deep notch on descending limb of main pulse derivative deflection is duplicated in Bcg. D, J.M., age 26, B.P. 120/65 mm. Hg, artificial valve substituted for aortic valve about 6 months before test to correct aortic regurgitation based on rheumatic heart disease. Note general similarity of the two records and that notch or flexure on the ascending limb of the pulse derivative shows on the I wave and in the ascending limb of J wave. E, M.C., age 37, B.P. 115/65 mm. Hg, nephritis with threatened uremia. B.P. formerly much higher. Note that abnormal wave in pulse derivative is reflected perfectly in Bcg. F, A.L., age 72, B.P. 155/90 mm. Hg, formerly pulmonary edema and greater hypertension. Again an abnormal notch in pulse derivative is accompanied by a corresponding abnormal wave in Bcg. G, M.R., age 60, B.P. 140/80 mm. Hg, former coal miner, moderate pneumoconiosis, angina pectoris (?). Before nitroglycerine note notch on pulse derivative and notch, slur, or flattening of J wave of Bcg. H, Same subject (M.R.), 3 minutes after 0.6 mg. of nitroglycerine under the tongue. Note disappearance of notch on pulse derivative and corresponding pointing of J wave of Bcg.

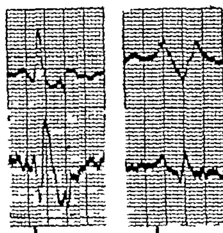


Fig. 3. Tracings selected to show how great the similarity of the two records may be and that this is true of certain distorted records as well as of normal records. Carotid pulse derivatives over ULF force Bcg, the pairs being selected to show maximum agreement. Black lines indicate onset of ejection in each subject. *Left.* Records of a healthy young adult, 23 years old. Note similarities of the two records and the marked deflections in each immediately after ejection begins. *Right.* Records of N. M., 25 years old, believed to have a cardiac myopathy. There was a history of rheumatic fever and prolonged disability. At a later date, operation was performed in the hope of correcting a mitral stenosis, but no valvular lesion was found. Note the similarity of pulse derivative and Bcg; note the lack of sharp deflections at the onset of ejection in both records, and their appearance near the end. These records indicate a greatly diminished positive acceleration of blood at the onset of ejection; maximum ejection velocity is attained abnormally late in systole and negative acceleration at the end of systole is unusually great.

Figs. 1 and 2 illustrate typical simultaneous records of the ULF force Bcg and the pulse derivative secured in 14 subjects. When inspecting these figures, one must remember that the Bcgs, calibrated before the test, have all been adjusted so that their amplitudes are directly comparable; but since the pulse derivatives had to be calibrated after the test, the amplitudes of these records can be compared only by means of the calibration given. The records reproduced in Fig. 3 were selected to show the degree of similarity between the two records seen occasionally in both normal and abnormal subjects.

Inspection of these figures shows that, over one half or more of the cardiac cycle the two records have a conspicuous resemblance. There is more respiratory variation in the Bcg than in the pulse derivative, and the resemblance between the two records reaches a maximum at one point in the respiratory cycle, e.g., in the third complex of Fig. 1,*A*, where the Bcg J, K, L, M, and N waves all have obvious analogues in the pulse derivative. Indeed, in the great majority of persons tested there is a *period of similarity* from the point where the IJ segment of the Bcg crosses the base line to the onset of the following G or H wave, in which the general resemblance of the contour of the two records is conspicuous, the large Bcg J wave and the sharp deflections at M and N closely resembling corresponding events in the pulse derivative.

In addition, Fig. 2 shows clearly that, when in any patient, an abnormality of the contour of one record is found within the period of similarity, the other record is often affected likewise.

The close relationship between the two records in the period of similarity is also clearly manifest in patients with extrasystoles or atrial fibrillation, the contour of the two records changing similarly from one beat to another. A similar relationship can be demonstrated in many cases after nitroglycerine, which is often followed by improvement in the contour of both records, as is shown in Figs. 2, *G* and *H*, and 4, and also by regression of both records as the action of this drug passes off.

But even when the correspondence within the period of similarity is at its best, one notes that the Bcg always shows small waves and high frequency phenomena not found in the pulse derivative, and that the more conspicuous events in the pulse precede corresponding events in the Bcg by an interval which, with one exception, ranged from 0.03 to 0.08 sec.

Outside the period of similarity there are constant differences between the contours of the two records. Examining Figs. 1, 3, 4, and 6, one notes that no equivalents to the pre-ejection waves of the Bcg (G and H) are seen in the pulse derivative. Also, when the two records are reproduced as in Figs. 1, 2, 3, 4, and 6, so that an increase in the velocity with which the pulse

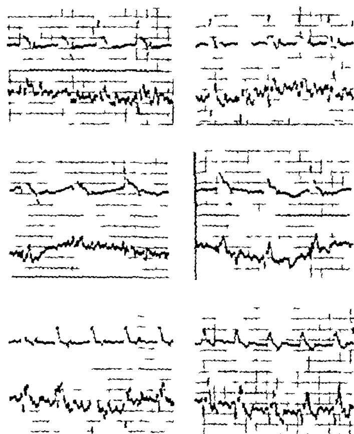


Fig. 4. Effect of nitroglycerine before (*left*) and after (*right*) 0.6 mg. had been placed under the tongue. The changes in blood pressure were small or negligible. Pulse derivatives above, U.L.F. force Bcg. *Top row*: M.R., age 60, B.P. 140/80 mm. Hg, coronary heart disease. *Middle row*: A.L., age 60, B.P. 130/80 mm. Hg, former cardiac infarct. *Bottom row*: W.W., age 43, B.P. 110/65 mm. Hg, pneumothorax. Note the marked increase in Bcg amplitude and improvement in contour, with smaller changes in pulse derivative.

pressure rises is recorded in the same direction as are the headward forces of the Bcg, the important I wave of the Bcg appears to have no equivalent in the pulse, although, as will be explained later, there is indeed a close relationship between them.

By studying the calibrations of both records as given in Figs. 1 and 2, one notes an important difference that is not obvious by inspection of the figures. The two records may be very similar in contour but very different in the relationship of their amplitudes to the normal. Indeed, when the amplitude of one of the two records is abnormally large, the other is often abnormally small. Thus, in many of our cases of hypertension the pulse derivative is of large amplitude although the force Bcg is small, as was found by Starr and Ogawa.[1,14] After nitroglycerine (Figs. 2 and 4) the amplitude of the Bcg is likely to increase, whereas that of the pulse derivative diminishes or remains the same, changes which are reversed as the action of the drug passes off.

Finally, as is shown in Figs. 1 and 6, in certain patients the usual similarity between the contours of the two records is lost or greatly distorted.

In 6 of the 16 patients who received nitroglycerine the improvement in the Bcg after the drug was very great, as is shown in Figs. 2 and 4; in only 2 of these patients had coronary heart disease been diagnosed. In 4 others the improvement was definite but less marked; only one of these had recognized coronary heart disease. In the remainder the drug caused no change in either record. Changes in blood pressure after the drug were small or absent.

The clinical and physiologic meaning of these findings will now be discussed

Discussion

Difficulties As has been known for years differences in the way the transducer is placed in relation to an artery may make large differences in the pulse record obtained and this formidable difficulty has been always in our thoughts We have guarded against it by recording the conventional pulse from several locations and using that place at which the record secured was the most nearly normal that we could obtain. Since Robinson[11] had found good agreement between conventional pulse records taken outside the carotid artery and those secured through a needle introduced into its lumen, we did not think that it was necessary to repeat this work, although because of our special interest in high frequency phenomena our apparatus and technique were different from his.

Our method of calibrating the carotid pulse derivative was not ideal since we used blood pressures determined in the brachial artery by the standard auscultatory technique as the basis for our measurement. There is certainly some difference between carotid and brachial pressures but it is not likely to be large. The ordinary errors of auscultatory measurements of blood pressure will also affect the result, but these errors are certainly small in comparison with the differences in blood pressure and its rate of change encountered in clinical work. Puncture of the carotid artery is not a simple procedure from the standpoint of either operator or patient. We believe that we used the best simple procedure available and that our calibration was good enough to permit us to detect the larger differences Since in this presentation the emphasis is on the contour of our pulse derivatives, and not on their amplitude, we were not stimulated to improve the calibration. It has long been the tradition of this laboratory to scrupulously avoid anything which might hurt or disturb the patients being tested and so alter the aspects of the circulation that we wished to measure.

When one records the derivative rather than the conventional pulse one secures certain *advantages* for respiratory variations of the base line and contamination from the venous pulse both low frequency phenomena, are largely filtered out of the records. The technique used was most satisfactory

Genesis of the relationship The surprising similarities seen in our records of the force Bcg and carotid pulse derivative turn one's attention to the physiologic relationship between these two aspects of the circulation. Certainly our two records are physically independent of one another indeed they have different dimensions, the forces of the circulation being altogether independent of the pressures existing

Results secured in experiments in which systole was simulated in cadavers and in which the curve of cardiac output at each instant of systole was accurately recorded indicate clearly that both pulse derivative[2] and force Bcg records[3] have their origin in this curve both being related to the acceleration with which blood is ejected This common origin explains the similarities seen in their contours we must also explain the differences

An explanation in the light of Noordergraaf's mathematical theory[12] was given by Starr and Ogawa[7] here we shall use a simpler model which although far from perfect mathematically has served to explain the main features of force and displacement Bcgs to many doctors not mathematically minded This model likens the force Bcg to the resultant of two groups of forces the first the footward reaction from cardiac ejection according to Newton's third law of motion the second the headward impact when the headward movement of ejected blood is largely stopped and in part reversed at the arches Both derived from the heart's energy these two forces are similar in contour but they are opposite in sign and the onset of one follows that of the other by an interval which represents the time required for the pulse wave to travel from the heart to and around the arches. When this time is shorter than their duration these forces will overlap for part of their course. Thus the Bcg their resultant can be divided into three parts first, a "pure" part in which the forces of reaction act alone second an "impure part in which

the forces of reaction and impact compete and partly neutralize one another and third a "pure" part in which the forces of reaction have largely ceased and those of impact act alone. The second "pure" part which has proved to be of longer duration than we had expected is what we see in our records as the period of similarity in it the contour of pulse derivative and that of force Bcg closely resemble one another. If such conceptions are reasonably correct one should be able to derive the complete contour of force Bcgs from that of the pulse derivative as follows.

Relationship of contour of pulse derivative to that of force Bcg. A typical systolic complex of a normal subject was selected; the Bcg amplitude was measured at intervals of 0.01 sec and redrawn to scale on coordinate paper as in Fig. 5,*A*. The pulse derivative recorded simultaneously was similarly measured but before it was redrawn the vertical dimensions were adjusted proportionately so that the main peak (*B*) conformed in amplitude to the tip of the Bcg J wave. This adjusted pulse derivative was now superimposed on the Bcg as in Fig. 5,*A*, the time relationships of both records remaining unchanged and their base lines coinciding.

Inspection of Fig. 5,*A* discloses that the initial instant of cardiac ejection identified by the beginning of the HI downstroke of the Bcg is followed after an interval of about 0.03 sec by the onset of the main wave in the pulse derivative; physiologically this interval is that required for the pulse wave to travel from the heart to the carotid artery.

Let us now compensate for this delay by moving the pulse derivative forward by that amount and redrawing it inverted with the main peak directed downward as in Fig. 5,*B*. This is our estimate of the contour of the forces of reaction which according to Newton's third law of motion would tend to move the body feetward as the blood was ejected from the heart headward. So this curve represents the contour of the forces which would be recorded by a force Bcg if at cardiac contraction the blood instead of turning at the arches was squirted out the head end of the body.

Resuming the inspection of Fig. 5,*A* one sees that in the period of similarity the corresponding features of the Bcg lag behind those of the derivative by about 0.03 sec. Physiologically this delay is due to the fact that the last forces recorded by the Bcg in each cardiac cycle have their genesis in the movement of blood taking place in the legs[13] and the interval is the difference between the times of arrival of the pulse in the carotid artery and in the vessels of the legs. To compensate for the delay let us now move the derivative to the right by that interval and record it without inversion as in Fig. 5,*B*. This curve is designed to represent the contour of the forces which have their origin in the impact of flowing blood thrown against the arches, and as blood decelerates at the end of systole.

If our model is reasonably correct the resultant of the two curves of Fig. 5,*B* should resemble the Bcg which we record

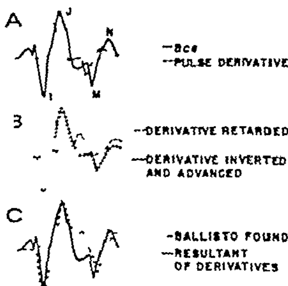


Fig. 5. Relationship of contour of ULF force Bcg to that of carotid pulse derivative. *A*. The two records from a normal young adult superimposed with their base lines coinciding and their amplitudes adjusted to coincide. The letters *I*, *J*, *M*, and *N* identify the Bcg waves. *B*. The pulse derivative advanced and inverted to represent the contour and amount of the cardiac footward recoil to ejection and the same curve retarded without inversion to represent the impact of moving blood strikes against the arches. *C*. The resultant of the two curves shown immediately above compared with the ULF force Bcg. Note close correspondence of contours.

in Fig 5 C one sees that the resemblance is close. The chief discrepancy the fact that the shoulder on the descending limb occurs nearer the wave tip in the pulse derivative although perhaps within our limit of error is often seen in records taken in the clinic in these abnormal notches, occurring both on the JK segment of the Bcg and on the corresponding part of the pulse derivative, tend to be closer to the wave tip in the latter We have no explanation for this difference at present Mathematically the resultant is a derivative of the original curve calculated with a finite time unit.

Deductions from this theory and observations which bear on it In this simplified conception each noteworthy feature of the cardiac ejection curve enters twice into the Bcg its second appearance being later in time and opposite in direction from its first hence, the large I and J waves of the Bcg when there is only one important wave in the pulse derivative. This theory also suggests that the contour of the initial part of the cardiac ejection curve would be best seen in the initial footward deflection of the Bcg the HI segment, during the *first pure period before the forces of* impact have begun and that the contours of the later part of the cardiac ejection curve would be best seen reversed in direction during the second pure period after the forces of reaction are largely over Between these two pure periods there would be an impure period during which the influence of the contour of the cardiac ejection curve would often be masked by the distortion from the competition between forces of reaction and of impact. But by examining the HI segment of the Bcg to learn about its onset and the JK area to learn about its end one learns a great deal if not all about the contour of the whole ejection curve

Observations *made on records* secured on our patients support this view for notches and other abnormalities found on the ascending limb of the main deflection of the pulse derivative the AB segment in the lettering of Starr and Ogawa[18] are *often accompanied by corresponding ab-*normalities on the HI segment of the force Bcg that is, on the advancing side of a wave directed footward as in *D* and *E* of Fig 6 On the other hand the common abnormalities seen on the decending limb of the main deflection of the pulse derivative the BC segment are best seen in the Bcg after the J wave tip on the declining side of a wave directed headward as shown in *F I J* and *K* of Fig 6

This simplified conception also explains why the period of similarity is so unexpectedly long If the cardiac energy were released in an explosive burst so brief that its effect was over before the blood was stopped and reversed in the arches, the Bcg would record the contour twice in *opposite directions, and without distortion* from the overlapping of competing forces.

Here a word of explanation is necessary for so many of our colleagues continue to think of the function of the heart as the Greeks thought of motion in general e.g., the sun is drawn by Apollo's chariot because, like a wagon on the earth if not continually worked upon its motion would stop. Similarly many think that the heart must keep pushing out the blood up to the end of ejection That this is not necessary has been clearly demonstrated by Spencer and Greiss[17] the data of Rushmer and associates[18] *are also consistent with* this new view The blood once set into motion will continue in motion because of its inertia until resistance stops it So, after positive acceleration is over and maximum velocity has been attained little if any cardiac effort will be required and this effort may cease well before the end of ejection Accordingly the important forces normally added during systole are of much briefer duration than the older conceptions led one to expect and the shorter their duration the shorter the "impure" period will be and the "pure" periods will increase in duration correspondingly until if the burst is brief enough the whole curve will appear in the Bcg *Also because in our model of the* genesis of the Bcg one reproduction of the cardiac ejection curve is placed behind the other in time (Fig 4) that portion of *both* curves hidden during the "impure" period will be much less than one might expect.

Judging from the contours of the Bcg and pulse derivative, the more important forces of cardiac ejection are to be found

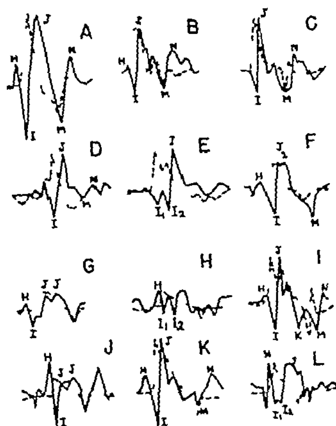


Fig. 4. Comparison of ULF force Bcg (*solid line*) and carotid pulse derivative (*broken line*) in various clinical conditions. In each subject a complex showing maximum agreement was selected. The two records were measured and redrawn with their base lines coinciding and their time relations unchanged, the amplitude of the derivative having been adjusted to make its maximum coincide with that of the Bcg. Note that the pulse derivative must be moved to the right to get maximum correspondence during the period of similarity. Small letters identify Bcg waves. *A*, H. C., age 23, B.P. 120/60 mm. Hg, a normal subject. The correspondence between the two records is typical of that found in healthy persons. *B*, M. C., age 37, B.P. 115/65 mm. Hg, uremia, former hypertension. Note close correspondence of contours, with same notch in both records. *C*, I. G., age 62, B.P. 165/95 mm. Hg, hypertension. Note close correspondence of contours, the J wave and the corresponding wave of the pulse derivative are both narrower than usual. *D*, K. P., age 20, B.P. 110/80 mm. Hg, rheumatic heart disease, mitral valvulitis. Note notch on HI segment and corresponding notch in pulse derivative; the relationship is best seen if the latter record is inverted. A left ventricular abnormality. *E*, A.S., age 71, B.P. 120/60 mm. Hg, mitral stenosis, atrial fibrillation, diabetes mellitus. Note doubled I wave reflected in corresponding distortion of pulse derivative; the relationship is best seen after inversion of that record. A left ventricular abnormality. *F*, L. B., age 17, B.P. 120/70 mm. Hg, rheumatic heart disease. Note flattened top of both Bcg J wave and pulse derivative. A left ventricular abnormality. *G*, T.S., age 49, B.P. 150/100 mm. Hg, hypertension (treated). *Note doubled I and J wave not reflected in derivative. The first I and J waves are of right ventricular origin.* *H*, M. N., age 79, B.P. 160/90 mm. Hg, former congestive heart failure. Note doubled I wave without reflection in pulse derivative; second tip probably right ventricular in origin. Delay in right ventricular forces suggests right heart failure. *I*, H. E., age 42, B.P. 140/80 mm. Hg, obesity, diabetes mellitus. Note deep notch on JK *segment duplicated in pulse derivative and indicating left ventricular incoordination.* *J*, B. K., age 58, B.P. 110/60 mm. Hg, history of three cardiac infarcts, angina pectoris, pneumoconiosis. Note great distortion of both records. Doubled J wave tip duplicated in pulse derivative. The evidence indicates weakness and incoordination of left ventricle and that the right is also abnormal. *K*, S.T., age 60, B.P. 195/90 mm. Hg, hypertension. Note notch on JK segment also appearing in pulse derivative and so indicating left ventricular incoordination. *L*, W. C., age 67, B.P. 115/70 mm. Hg, right pneumonectomy for carcinoma of lung, former congestive failure, right bundle branch block. Note distortion of Bcg not found in pulse derivative. Notches on I and J waves are of right ventricular origin.

in healthy persons, in the first third of ejection. On this fact Starr and Ogawa[7] based their explanation of the similarity between force Bcg and brachial pulse derivative which they found in healthy persons, and the results secured in this study support this view. But Starr and Ogawa failed to find close similarity between their two records in many persons with heart disease. This lack of correspondence was attributed to the fact that when the heart was weak, the blood was accelerated more slowly, the forces reached their maximum later and so were of longer duration, and the "pure" parts of the Bcg were reduced in length. Although this is doubtless true in certain cases, our results have proved that it is not the chief explanation for the failure of Starr and Ogawa to find good correspondence between the two records in the sick. By using the carotid pulse we have greatly improved the correspondence in the sick; thus, Starr and Ogawa failed to find it because of distortion of the pulse as it traveled down the vessels to their transducer on the brachial artery. The average age of their patients with cardiac disease was much greater than that of the healthy young adults in whom the correspondence was good, and the vascular changes of aging doubtless increased the distortion. The nearer to the heart the pulse is sampled the better the correspondence of its derivative with the force Bcg.

The smaller differences between the two records are readily explained. The far greater content of small waves and high-frequency information usually seen in the Bcg is due to more than one factor. The difference in time of the opposing forces, as is illustrated in Fig. 5,*B*, causes the small waves of the forces of the cardiac ejection curve to appear twice in the resultant, the Bcg. In addition, the Bcg is more subject to artifacts from movement of the patient, and from vibrations in the building, than is the pulse record. Finally, high-frequency components are quickly damped out of the pulse as it travels.

The small differences in degree of similarity seen during the respiratory cycle are due to the varying contribution of the right heart to the Bcg as its filling increases and diminishes during that cycle, the Bcg contour being most similar to that of the pulse derivative when the contribution of the right heart is minimal.

Clinical interpretations. An understanding of the physiologic background of the similarities and differences found in the two records puts one in a position to discuss the clinical significance of our findings, and although one can see a great deal by inspection alone, the important factors are more easily demonstrated if the two records are superimposed according to the technique described. Examples secured in 12 of our patients, typical of our experience, are given in Fig. 6. From such data our cases can be readily divided into three main groups according to the normality of the two records and their relationships to one another.

In the first group, both records are normal in contour and the two have their usual close resemblance to one another during the period of similarity. All the healthy young adults tested have fallen into this group, and it will not be discussed further. Figs. 3(*left*), 5,*A*, and 6,*A* are good examples.

In the second group, both records are abnormal in contour but they continue to have a close resemblance to one another. In most cases this resemblance is seen in the period of similarity, as in Figs. 3(*right*) and 6,*B*, *C*, *F*, *I*, *J*, and *K*; in others, when the abnormalities appear earlier, one sees that after inversion of the derivative the changes in its contour resemble those of the I wave, as in *D* and *E* of Fig. 6. In such cases, one concludes that the incoordination of the cardiac contraction has its origin in an abnormality of the left ventricle. In our experience, such evidence of left ventricular abnormality has been found only in certain elderly persons and in certain patients suffering from obvious heart disease.

In the third group, the Bcg contour is plainly abnormal but that of the pulse derivative is normal, as in *G*, *H*, and *L* of Fig. 6, and the significance of this finding requires more extended discussion.

Although it contributes far less than does the left heart to the Bcg, the contribution of the normal right heart is by no means negligible.[11] In normal conditions it contributes about one half of the I wave and

a smaller proportion of the J wave. One cannot say that the right ventricle plays no part in the contour of the carotid pulse derivative for forces would be so readily transmitted through the ventricular septum, but certainly the effect of right ventricular forces would be far greater on the Bcg than on the carotid pulse. We believe, therefore, that the explanation of these distorted Bcg contours found when the pulse contour is normal is to be sought in an abnormal asynchronism of the forces of the right and left ventricles. Indeed, we have been so bold as to indicate in Fig. 6,G, H, and L places at which we believe that the abnormal right ventricular forces have distorted the Bcg contour.

We have encountered this type of abnormality only in cases of obvious pulmonary disease or in cases of systemic hypertension. In either instance it is easy to see that weakness of one ventricle, or abnormal counterpressure to its ejection, might delay the forces of that side so that their normal synchronism with the forces of the other ventricle was lost and the Bcg correspondingly distorted. Which of the two ventricles is at fault can usually be determined by the time correspondence with the pulse derivative, which identifies the left ventricular components, and it seems to be reasonable to suppose that other distortions seen in the Bcg have a right ventricular origin. In some records the confusion is so great that a diagnosis of incoordination of both ventricles seems to be warranted.

No representative of a possible fourth group, in which the Bcg is normal but the pulse derivative abnormal in contour, has been encountered in this study. Starr and Ogawa encountered only one possible case in which they suspected that the abnormality found in the pulse derivative was due to an artifact. It should be noted that the absence of cases of this kind is in accord with our views concerning the relationships between the two records.

The ability of nitroglycerine to improve the Bcg of many elderly persons, both with and without recognized coronary heart disease, was noted by Starr, Pederson, and Corbascio[11] using a HF Bcg. This finding has been confirmed in this study using more modern equipment, and also by others.[18] Starr, Pederson, and Corbascio also found some patients in whom nitroglycerine caused the Bcg to deteriorate. No Bcg which deteriorated after the drug was recorded in our short series, but one of our subjects suffered from a brief spell of weakness during its action; unhappily, no Bcg was taken at this time.

Finally, we must point out that the taking of simultaneous records of the Bcg and pulse derivative opens up many new approaches to quantitative studies of the cardiodynamics of our patients. The information provided by one record supplements that of the other; the pulse, a pressure record, is related to the potential energy in the vessels at any instant; the Bcg is related to flow and, thus, to the kinetic energy. The sum total of this energy has been put into the vessels by the heart, so that, given knowledge of both aspects, one has a better knowledge of total cardiac performance than is possible from either record alone. How best to combine the quantitative information provided by the two records into a single estimate of cardiac performance presents some fascinating theoretical problems far beyond the scope of this study. But our results show clearly that in some patients the quantities measured in both records are increased, in other patients they are both diminished, and in still others the pulse derivative is large when the Bcg is small and vice versa.

The unexpected similarities between the contours of the two records used in this study confirm the results of cadaver experiments with regard to the aspects of cardiac function to which they are most closely related.[3,4] Thus, both force Bcg and pulse derivative are related to the acceleration aspects of cardiac ejection[3,4]; the data which they provide throw light on this aspect of cardiac performance. The velocity Bcg and the conventional pulse should be studied together in order to throw light on the velocity aspect of cardiac function; the displacement Bcg and the area under the conventional pulse wave would throw light on the displacement aspect. To combine information relating to different aspects of cardiac function is to risk confusion.

The two records, as we have used them also permit an estimate of pulse wave velocity The onset of ejection is clearly marked by the beginning of the HI downstroke in the Bcgs of most patients the time of arrival of the pulse in the carotid artery is usually clearly evident in the pulse derivative Unfortunately the distance is short, the travel time correspondingly brief and unavoidable errors in the recording have no little effect on such an estimate. Pulse wave velocity also manifests itself at the end of the record where the terminal deflections, MN in the Bcg and DE in the pulse are usually clearly marked their difference in timing indicates the difference between the times of arrival of the tail of the pulse wave in the carotid artery and in the vessels of the legs We believe that large abnormalities of pulse wave velocity can be readily recognized in our records by inspection. This observation not only adds to our knowledge of the state of the vessels, but also provides information of value in the interpretation of Bcgs for pulse wave velocity is certainly a factor in the relationship of the amplitude of these records to cardiac function how large a factor is debatable.

In short, these two records, when taken simultaneously provide a mass of information about myocardial function which is not disclosed by the routine cardiac examination used today and they provide it without danger or discomfort to the patient and after the apparatus is set up at little expense.

Summary

Simultaneous records of ULF force Bcgs and the *carotid* pulse derivative have been taken on 100 patients and healthy persons In all of the healthy persons tested and in the majority of the patients the resemblance between the contours of these two records was very strong during a considerable part of the cardiac cycle This resemblance was much stronger than that found by Starr and Ogawa, who compared the force Bcg with the *brachial* pulse derivative

The resemblance of the two records is attributed to a common origin in the time course of the blood delivered to the circulation during the cardiac contraction The differences found between the contours of the two records are in accord with knowledge of their different geneses.

Many examples were found in which a striking abnormality of the contour of the pulse derivative was accompanied by a closely comparable abnormality of the Bcg a finding indicating an incoordination of the left ventricular contraction. When Bcg abnormality was not accompanied by a corresponding alteration of the carotid pulse derivative, abnormality of right heart function or asynchronism of the forces of the right and left sides of the heart was suspected a different type of cardiac incoordination In some cases the confusion of the records suggests an incoordination of both the right and left sides of the heart.

Abnormalities of cardiac coordination were encountered frequently In our series of 84 ambulatory patients 29 per cent were judged to have incoordination of the left ventricle and 14 per cent to have asynchronism of the forces of the two sides of the heart. These abnormalities were found not only in patients suffering from cardiac disease detected by conventional methods, but also in certain elderly persons in whom the routine cardiac study was negative Abnormalities of this kind have not been encountered in healthy young adults

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Hemodynamic consequences of atrial and ventricular arrhythmias in man

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Certain cardiac arrhythmias occur commonly in patients with or without cardiovascular disease. Because of their fleeting and intermittent nature, very little is known of the effects of these arrhythmias on cardiac function in man since accurate measurements of cardiac output and other parameters are difficult to obtain.

It is the purpose of this report to describe the hemodynamic consequences of certain atrial and ventricular arrhythmias in man.

Material and methods

Thirty-two patients who exhibited some form of atrial or ventricular arrhythmia were studied. All but 5 had evidence of heart disease by clinical or laboratory evidence. Among the normal subjects, one had Wolff-Parkinson-White syndrome. Cardiac output was determined by the indicator-dilution technique, using indocyanine green as an indicator.[1-4] Measurements of cardiac functions were made during the episode of cardiac arrhythmia and after conversion to sinus rhythm, the exception being in patients with permanent heart block.

Details of our technique have been described in previous reports.[1-3] Approximately half of the subjects underwent cardiac catheterization, and the indicator was injected into the right ventricle for determination of cardiac output. In the remainder of the subjects the indicator was injected into the left antecubital vein. Sampling was from the right brachial artery in all cases. In our earlier studies the Stewart-Hamilton formula was used for calculation of the cardiac output, but more recently we have used a computer[4] coupled to a Gilford densitometer for electronic computation of the area encompassed by the dye curves.

Pressures were recorded with a P23Db Statham pressure transducer and the mean pressure was obtained by electronic filtering. Peak derivative of the brachial arterial pressure, i.e., dp/dt, was obtained using an R-C differentiating circuit. Mechanical systole was measured as the interval between the first vibration of the first heart sound and the beginning of the aortic component of the second sound as shown on a phonocardiogram recorded at the mitral area.[5] Ejection time was measured from

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the indirect carotid tracing obtained with a Sanborn No. 374 linear crystal microphone. Ejection time minus mechanical systole was taken as the period of isometric contraction. Peak systolic pressure was used in Sarnoff's formula[7] to calculate the tension time index. The tracings were recorded on the Electronics for Medicine recorder at a paper speed of 200 mm. per second with 20-msec. time lines. Exercise studies were obtained using a calibrated bicycle ergometer. All the studies were performed with the subjects in a supine position.

Results and comments

I. Atrial arrhythmias

1. ARTIFICIALLY INDUCED ATRIAL TACHYCARDIA. Six patients with normal sinus rhythm were paced from the right atrium at rapid rates with a bipolar electrode catheter connected to an external pace-

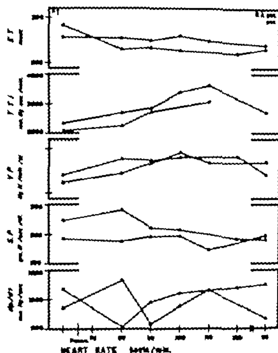


Fig. 2. Ejection time (*E.T.*), tension-time index (*T.T.I.*), ventricular power (*V.P.*), stroke power (*S.P.*), and the first derivative of brachial arterial pressure (*dp/dt*) during artificially induced atrial and ventricular tachycardia in one normal subject. See Fig. 4.

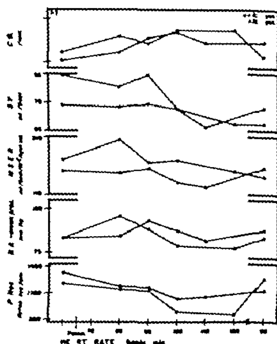


Fig. 1. Cardiac output (*C.O.*), stroke volume (*S.V.*), mean systolic ejection rate (*M.S.E.R.*), mean pressure (*B.A. mean pres.*), and peripheral resistance (*P. Res.*) during artificially induced atrial and ventricular tachycardia in one normal subject. The control heart rate for the atrial pacing was 70 beats per minute, and for the ventricular pacing 60 beats per minute. The remainder of the hemodynamic data are illustrated in Fig. 5.

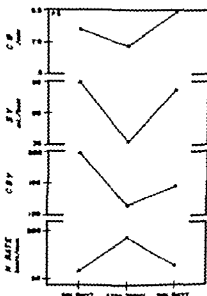


Fig. 3. Cardiac output (*C.O.*), stroke volume (*S.V.*), central blood volume (*C.B.V.*), and heart rate (*H. Rate*) in one patient before, during, and after atrial tachycardia.

maker. Three had a normal heart, and 3 had heart disease but only one showed evidence of congestive heart failure. The atrial rate was increased from a base line control figure of 50 to 75 beats per minute to a maximum of 120 beats per minute. As the rate rose the cardiac output, mean systemic pressure, tension time index, ventricular power and stroke power rose, reaching their maximum values at 100 beats per minute. At the same time, stroke volume, right ventricular systolic pressure, and the first derivative of brachial arterial pressure remained unchanged whereas the peripheral resistance and ejection time decreased (Figs. 1 and 2). At faster rates, cardiac output decreased slightly and there was a greater decrease in stroke volume, peripheral resistance, ejection time, and stroke power. However, systemic pressure, tension time index, and ventricular power continued to rise. The changes observed for the group are illustrated in one case in Figs. 4 and 5.

It was interesting to observe that the response of the cardiac output and other

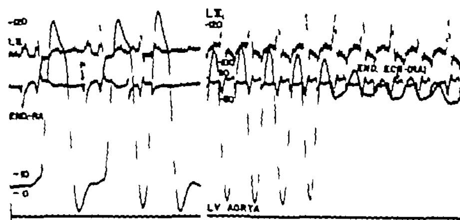


Fig. 4. Left ventricular pressure curves in a patient with sinus rhythm and during an episode of atrial tachycardia. The hemodynamic findings in this patient are illustrated in Fig. 1.

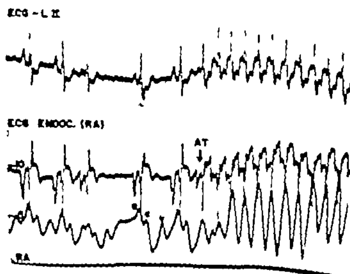


Fig. 5. Right atrial pressure curves in a patient with sinus rhythm and during an episode of atrial tachycardia. The hemodynamic findings in this patient are illustrated in Fig. 1.

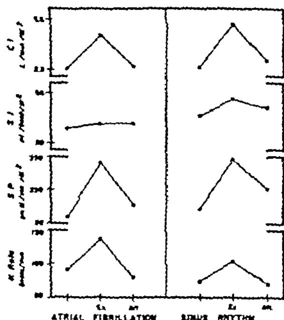


Fig. 6. Average cardiac index (*C.I.*), stroke index (*S.I.*), stroke power (*S.P.*), and heart rate (*H. Rate*) at rest, and during and after exercise during atrial fibrillation and after conversion to sinus rhythm.

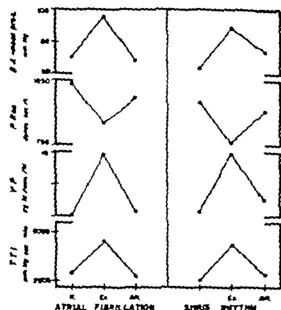


Fig. 7. Average brachial arterial mean pressure (*B.A.-mean pres.*), peripheral resistance (*P. Res.*), ventricular power (*V.P.*), and tension-time index (*T.T.I.*) at rest, and during and after exercise during atrial fibrillation and after conversion to sinus rhythm. See Fig. 6.

parameters to artificial pacing was qualitatively identical to that observed for ventricular pacing (Figs. 1 and 2).

2. PAROXYSMAL ATRIAL TACHYCARDIA. Hemodynamic studies were made in a 22-year-old man with Wolff-Parkinson-White syndrome who developed during cardiac catheterization an episode of paroxysmal atrial tachycardia which reverted spontaneously to sinus rhythm. Base line data had been obtained prior to the development of this arrhythmia. During the episode of tachycardia the heart rate rose to 180 beats per minute, the cardiac output decreased from 7.42 to 6.90 L. per minute (a decrease of 8 per cent), and the stroke volume fell from 95 to 38 ml. per beat (a decrease of 60 per cent). The central blood volume decreased slightly (Fig. 3). The left ventricular systolic and end-diastolic pressures did not change significantly during the episode of tachycardia (Fig. 4). The average ventricular power decreased by 7 per cent, and the right atrial pressure increased from 5 to 10 mm. Hg (Fig. 5).

3. ATRIAL FIBRILLATION. Eight patients who had atrial fibrillation which was successfully converted to sinus rhythm with an external direct-current shock[4] were studied. Four of them had rheumatic heart disease with mitral involvement, and there were single instances of arteriosclerotic heart disease, hyperthyroidism, Paget's disease, and idiopathic atrial fibrillation. The patients were studied at rest and during exercise before and after conversion to sinus rhythm. Postconversion studies were obtained 30 minutes after conversion to sinus rhythm and repeated again in 4 patients 5 to 30 days after the initial procedure.

The cardiac index for the group at rest was at the lower limits of normal prior to conversion, with an average for the group of 2.86 L. per minute per square meter. After conversion to sinus rhythm this parameter did not change significantly and averaged 3.05 L./min./M.[2] (an increase of 6 per cent). During exercise the cardiac index increased in both preconversion and postconversion studies, and again the difference was not significant (Figs. 6 and 7).

Other parameters showed significant changes. After conversion, the stroke index increased 22 per cent at rest and 30 per

cent during exercise heart rate slowed by 16 per cent at rest and was 24 per cent slower during exercise mean arterial pressure was 10 per cent lower at rest and rose less with exercise peripheral resistance at rest dropped 12 per cent and 17 per cent during exercise ventricular power at rest decreased 18 per cent stroke power decreased by 13 per cent and the tension-time index decreased 58 per cent. The figures obtained several days after conversion to sinus rhythm were essentially identical with those obtained immediately after conversion (Figs 8 and 9)

COMMENTS Experimentally induced atrial tachycardia[9-12] in dogs results in a significant fall in the mean systemic arterial pressure atrial pressures, cardiac output, and stroke volume. Corday and Irving[11] have also shown that, in experimental atrial tachycardia, when the ventricular rate exceeded 190 per minute, the systemic pressure, cardiac output cerebral renal, and mesenteric blood flow decreased significantly In addition this arrhythmia resulted in a 25 to 35 per cent decrease in the coronary blood flow [11] However Wegria and associates[13] and Maxwell and associates[11] have shown variable changes in the coronary flow during this arrhythmia.

Cotton demonstrated elevated levels of catecholamines in the blood of dogs with experimentally induced atrial tachycardia McIntosh and associates[17] postulated that this increase in catecholamines might have resulted from a decrease in the mean arterial pressure and pulse pressure which in turn stimulates the baroreceptors and results in sympathetic stimulation and the secretion of catecholamines.

An elevation of the atrial pressure is a part of the hemodynamic findings in experimental supraventricular arrhythmias (Fig 3) This probably results from a shortening of ventricular diastole as well as from the occurrence of atrial systole partially or completely while the atrioventricular valves are still closed The contour of the atrial pressure curve in atrial tachycardia is often characterized by a single wave form as demonstrated in Fig 3 Nakano[9] has shown that the above described hemodynamic effects are almost indistinguishable from those of ventricular tachycardia except that the effects ob-

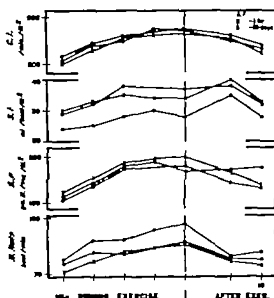


Fig 8 Cardiac index (*C I*) stroke index (*S.I*) stroke power (*S.P*) and heart rate (*H Rate*) at rest, and during and after exercise in one patient during atrial fibrillation, 1 hour and 21 days after conversion to sinus rhythm. See Fig 9

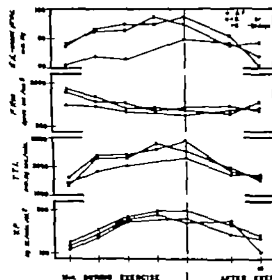


Fig 9 Mean brachial arterial pressure (*B.A.-mean press.*), peripheral resistance (*P Res*) tension-time index (*T T I*) and ventricular power (*V.P*) at rest, and during and after exercise in one patient, during atrial fibrillation, 1 hour and 21 days after conversion to sinus rhythm. See Fig 8.

served with ventricular tachycardia are always greater than those which follow atrial tachycardia of an equivalent rate.

Only a few studies have been made of the hemodynamic consequences of supraventricular tachycardia in man. Saunders and Ord[1] demonstrated in 3 patients with Wolff-Parkinson-White syndrome that during the episode of tachycardia there was a significant decrease in the systemic pressure with little change in the peripheral resistance and in the cardiac output. The stroke volume fell markedly during tachycardia and there was also a prompt rise in pulmonary arterial and wedge pressures. These observations had been made previously by Ferrer and co-workers[illegible] in 2 patients with Wolff-Parkinson-White syndrome who developed nodal tachycardia during cardiac catheterization.

Our studies in one patient with spontaneous atrial tachycardia confirm the above-mentioned findings (Fig. 1). In addition, in the group with artificially induced atrial tachycardia, both in patients with normal hearts and in those with heart disease, the changes observed were somewhat similar to the ones described with spontaneous tachycardia. In this group of patients a stepwise increase in heart rate resulted in a stepwise rise in the cardiac output, tension-time index, and ventricular power with a decrease in the ejection time, peripheral resistance, stroke power, mean systolic ejection rate, and systemic pulse pressure (Figs. 4 and 5). There were no significant changes in the first derivative of the brachial arterial pressure, stroke volume, right ventricular pressure, and isometric contraction time.

Studies describing the hemodynamic consequences of converting atrial fibrillation to sinus rhythm with direct-current shock in man are just now becoming available. Oram and associates[illegible] studied 10 patients who showed no significant changes in cardiac output shortly after conversion to sinus rhythm. However, there was a 70 per cent increase in cardiac output in the repeated studies performed several days after conversion to sinus rhythm. Our findings in 5 cases also did not show any changes in the cardiac output in the resting figures after conversion to sinus rhythm. During exercise, the cardiac output rose in both groups, but patients with sinus rhythm had a greater increase in the stroke volume and a lesser degree of rise in the heart rate (Figs. 6 and 7). Studies repeated several days (Figs. 8 and 9) after conversion to sinus rhythm failed to reveal any significant improvement in the cardiac output as described by Oram. Our observations are therefore in agreement with

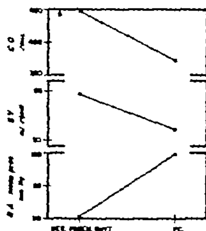


Fig. 10. Cardiac output (C.O.), stroke volume (S.V.), and mean brachial arterial pressure (B.A. mean pres.) in one patient with complete heart block and an artificial pacemaker rhythm. Reg. Pacem. Rhyt., Regular pacemaker rhythm. V.P.C., Multiple ventricular premature contractions.

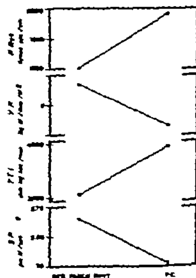


Fig. 11. Peripheral resistance (P. Res.), ventricular power (V.P.), tension-time index (T.T.I.), and stroke power (S.P.) in the same patient as in Fig. 10.

those of Boer and associates[22] and Gruettinger and associates,[23] whose studies also failed to demonstrate improvement in the cardiac output after conversion to sinus rhythm

The explanation for the lack of a significant increase in cardiac functions after conversion of atrial fibrillation to sinus rhythm is not clear Bramwell and Jones,[24] in 1944, developed the concept of atrial failure, and they indicated that a diseased atrium may not be able to perform its function adequately Therefore, it is conceivable that the restoration of coordinated atrial contraction in these patients may indeed be of no great benefit to cardiac function This concept of atrial failure has been recently revised by Mitchell Gilmore and Sarnoff[25] Braunwald[26] has also shown that the atrial contraction waves are so diminutive in many patients with long-standing heart disease and atrial fibrillation that it is unlikely that these weak atrial contractions may significantly influence ventricular filling when restoration of sinus rhythm is accomplished

II Ventricular arrhythmias

1 MULTIFOCAL VENTRICULAR PREMATURE CONTRACTIONS Three cases were studied which demonstrated the presence of several ventricular premature contractions, during the determination of the cardiac output with spontaneous reversion to a regular rhythm These 3 patients had complete heart block and the ventricular rate was being controlled by means of an electrode catheter placed in the right ventricle and connected to the output of an external pacemaker The findings illustrated in Figs. 10 and 11 were typical for the group.

With a regular and fixed ventricular rate the cardiac output was 4.5 L. per minute. When the patient developed multiple premature beats the cardiac output fell to 3 71 L. per minute (a decline of 21 per cent) At the same time, stroke volume decreased by 18 per cent. Mean systemic arterial pressure peripheral resistance and tension time index increased whereas ventricular power and stroke power remained the same (Figs. 10 and 11) Since a number of "regular" beats failed to appear heart rate stayed about the same

2 BIGEMINAL RHYTHM Two patients with complete heart block and permanently implanted pacemakers developed temporary bigeminal rhythm during the course of a study with spontaneous reversion to a regular rhythm

Base-line data had been obtained prior

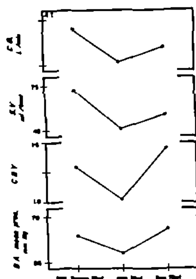


Fig. 12 Cardiac output (*C O*) stroke volume (*S V*) central blood volume (*C.B V*) and mean brachial arterial pressure (*B A mean pres*) in one patient with complete heart block during regular pacemaker rhythm and during bigeminal rhythm See Fig. 13

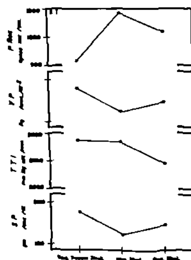


Fig. 13 Peripheral resistance (*P Res.*) ventricular power (*V.P*) tension-time index (*T T.I*) stroke power (*S P*) in the same patient

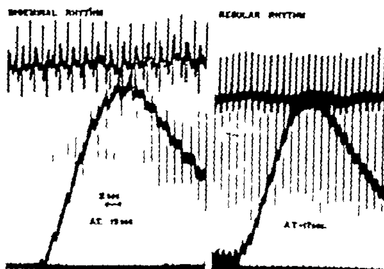


Fig. 14. Dye-dilution curves obtained in the same patient as in Fig. 12 recorded during bigeminal rhythm and during the regular pacemaker rhythm.

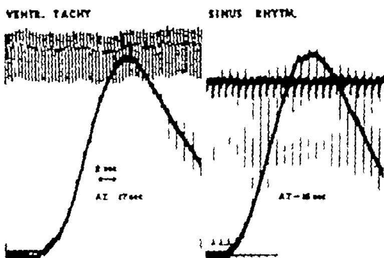


Fig. 15. Dye-dilution curves obtained in a patient during spontaneous ventricular tachycardia and after conversion to sinus rhythm. See Figs. 16 and 17.

to development of the bigeminal rhythm. During the period of this arrhythmia the cardiac output fell from 5.39 to 3.17 L. per minute (42 per cent), and the stroke volume decreased from 73 to 47 ml. per beat (a decrease of 36 per cent). The central blood volume, mean systemic pressure, ventricular power, and stroke power fell 24, 10, 39, and 35 per cent, respectively. The mean circulation time increased by 24 per cent, and the peripheral resistance increased by 54 per cent (Figs. 12, 13, and 14). There was also a significant variation in the pulse pressure. The "regular" pacemaker beat had an average peak systolic pressure of 110 mm. Hg, with little variation from one beat to another, whereas the spontaneous ectopic beats had significant beat-to-beat variation, with the peak systolic figures in the range of 73 to 95 mm. Hg. The ectopic beats produced a peripheral pulse of sufficient magnitude to result in palpable pulse and measurable pressure. Nevertheless, this abnormal rhythm was

associated with a significant disturbance in cardiac function as demonstrated by the above-mentioned figures.

3 SPONTANEOUS VENTRICULAR TACHYCARDIA. A 61 year-old patient with arteriosclerotic heart disease who developed a ventricular tachycardia which was converted to regular sinus rhythm with the use of a D C defibrillator was studied The studies were repeated 4 days later when ventricular tachycardia recurred The cardiac output was below the limits of normal during the ventricular tachycardia (3 92 L. per minute) with a marked reduction in stroke volume to 27 ml per beat. The heart rate was 144 beats per minute (Fig 15) Conversion to regular sinus rhythm resulted in no significant change in cardiac output peripheral resistance, and ventricular power The stroke volume, ejection time and stroke power increased by 70 24, and 40 per cent respectively Heart rate, mean arterial pressure, and tension time index decreased by 56 4 and 35 per cent, respectively (Figs. 16 and 17) Variations in the peripheral pulse pressure were present, with changes in the systolic pressure of greater magnitude than those observed in the diastolic pressure. This same type of response was reproduced in the second study

4 COMPLETE HEART BLOCK AND ARTIFICIAL PACING Cardiac functions were determined in 18 patients with complete heart block in whom an ectopic right ventricular focus at various fixed frequencies was induced by means of an electrode catheter placed in the right ventricle and connected to an external pacemaker At a fast ventricular rate this type of rhythm is somewhat identical to ventricular tachycardia. These patients were studied at slow ventricular rates and during progressive increases in heart rate to a maximum of 125 beats per minute

At a slow ventricular rate the cardiac output was abnormally low The right atrial pressure right ventricular systolic pressure, pulmonary and systemic resistances, stroke volume, and ejection time were significantly increased above the normal figures. With an increase in the rate of ventricular stimulation a bell shaped type of curve was obtained with a peak response occurring at a rate of

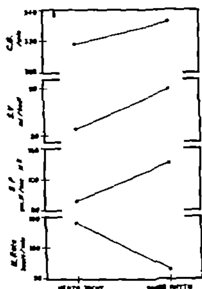


Fig 16 Cardiac output (*C.O*) stroke volume (*S.V*) stroke power (*S.P*) and heart rate (*H Rate*) during ventricular tachycardia and after conversion to sinus rhythm. See Fig 17

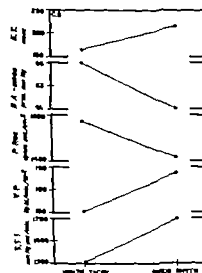


Fig 17 Ejection time (*E T*) mean brachial arterial pressure (*B.A* -mean) peripheral resistance (*P Res*) ventricular power (*V.P*) and tension-time index (*T T I*) during ventricular tachycardia and after conversion to sinus rhythm. See Fig 16

stimulation in the range of 62 to 93 beats per minute (average of 76 beats per minute—Figs. 18 and 19) At this range of rate the cardiac index and the mean systemic arterial pressure increased by 67 and 15 per cent, respectively The stroke index d

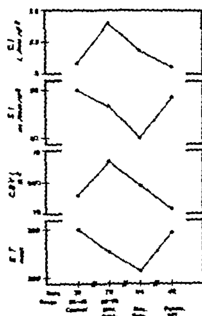


Fig. 18. Average cardiac index (C.I.), stroke index (S.I.), central blood volume index (C.B.V.I.), and ejection time (E.T.) in a group of 18 patients with complete heart block. *Max. Resp.*, Maximal response. *Max. Rat.*, Maximal rate of pacing. *Pm. on Off*, Pacemaker off. See Fig. 19.

creased by 20 per cent. There was also a decrease in the peripheral resistance and an increase in the ventricular power in relation to the control figures obtained at slow rates. A further increase in the rate of artificial ventricular stimulation (maximum rate of 125 beats per minute) beyond the peak response resulted in a 27, 50, 70, and 22 per cent decrease, respectively, in the cardiac index, stroke index, average ventricular power, and ejection time as compared with the figures obtained at the point of maximal response (average rate of 76 beats per minute). At the same time the peripheral resistance and mean circulation time increased by 50 and 19 per cent, respectively.

The contribution of atrial systole to the cardiac functions could be studied in these patients because atrial systole occurred at various intervals during the cardiac cycle. It was shown that when atrial systole occurred 1 to 300 msec. away from ventricular systole, the ejection time, first derivative of the brachial arterial pressure, tension time index, and brachial arterial

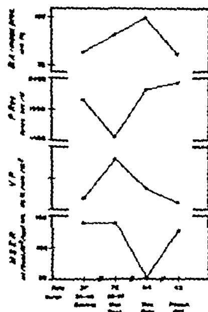


Fig. 19. Average brachial arterial mean pressure (*B.A.-mean pres.*), peripheral resistance (*P. Res.*), ventricular power (*V.P.*), and mean systolic ejection rate (*M.S.E.R.*) in a group of 18 patients with complete heart block. (The legend is the same as that in Fig. 18.)

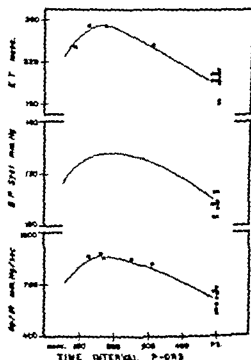


Fig. 20. Ejection time (*E.T.*), brachial arterial systolic pressure (*B.P. Syst.*), and first derivative of the brachial arterial pressure (*dp/dt*) as a function of the P-R interval.

systolic pressure increased by 13, 14, 33, and 12 per cent, respectively, as compared to when atrial systole occurred during ventricular systole (Fig. 20).

5. VENTRICULAR TACHYCARDIA IN NORMAL HEARTS. Four normal subjects were studied and the ventricular rate was controlled by means of an electrode catheter placed in the right ventricle and connected to an external pacemaker. The heart rate was increased from the base-line rate of 60 to 90 beats per minute to a maximum of 125 beats per minute. At the base line rate the cardiac output, stroke volume, systemic pressure, peripheral resistance, tension time index, ventricular power and dp/dt of the brachial arterial pressure were within normal limits. A stepwise increase in heart rate resulted in a stepwise increase in cardiac output and peripheral resistance. The stroke volume, systemic systolic arterial pressure, ejection time, stroke power, average ventricular power, mean systolic ejection rate, and first derivative of the brachial arterial pressure fell significantly. The brachial arterial diastolic pressure and mean pressure, right ventricular systolic and diastolic pressures, tension-time index, and isometric contraction time did not change significantly (Fig. 5).

COMMENTS. Multiple ectopic beats decrease cardiac output because they occur at times in the cardiac cycle when ventricular filling is inadequate to yield a good stroke volume. Variations in atrial pressure result from regurgitant beats and might account for the sensation of pulsations, fullness or throbbing in the neck felt by these patients. A vigorous ventricular contraction with a large stroke volume which follows a premature contraction most likely is responsible for the palpitation referred to by these patients. The reduction in stroke volume, pulse pressure, and cardiac output which accompanies ventricular ectopic beats may precipitate congestive heart failure in a borderline compensated heart, such as might occur after acute myocardial infarction. It is unlikely that this would ever happen in a normal heart, however.

It has been shown previously by Wiggers[17] that in normal hearts, ventricular filling takes place most effectively and rapidly during the early part of diastole. This period of rapid ventricular filling begins immediately after the opening of the atrioventricular valve and lasts approximately 80 to 140 msec., as demonstrated in the apexcardiogram.[18] As the heart rate increases and diastole becomes shorter, rapid ventricular filling and, thus, stroke volume and cardiac output will be progressively impaired. In fact, Rushmer and associates[19] demonstrated that an increase in heart rate results in a significant decrease in the systolic and diastolic volume of the ventricles.

Experimental studies in dogs by Nakano[9] and others have shown that a stepwise increase in heart rate in ventricular tachycardia is associated with a stepwise decrease in mean arterial pressure, stroke volume, and cardiac output, and a stepwise increase in pulmonary arterial pressure, left and right atrial pressures, and pulmonary and peripheral resistances. The decrease in the ventricular function curves seen under these circumstances is also indirectly related to the impairment of myocardial contraction that results from tachycardia induced hypoxia of the heart.[20,21]

Duff and associates[22] and Starzl and associates[23] demonstrated that in dogs with complete heart block in which the heart rate was controlled by means of electrical stimulation of the ventricles, the cardiac work increased with the heart rate, reaching a maximum between 120 and 180 beats per minute and then decreased at higher rates. At rates above 200 beats per minute the cardiac output and systolic, diastolic, and mean systemic pressures decreased. The atrial pressures also rose at this level of rate. Our observations in patients with complete heart block indicate that the peak response of cardiac output to electrical stimulation of the ventricle occurs at rates in the range of 62 to 93 beats per minute (average of 76 beats per minute). This early peak response is most likely related to the fact that these patients with complete heart block are operating at the peak of their cardiac reserve and therefore do not tolerate well great decreases in the diastolic filling time. Thus, any further rise in the rate beyond the critical period of filling time results in prompt elevation of the atrial and ventricular pressures, with a decline in volume and cardiac output. In ...

observation is confirmed by our studies performed in normal subjects in whom artificial and temporary acceleration of the heart rate was accomplished by means of an electrode catheter placed in the right ventricle. Their peak response in cardiac output occurred at a faster ventricular rate than that in the group with diseased hearts. Thus ventricular tachycardia is an arrhythmia of serious hemodynamic consequence in patients with heart disease because it usually precipitates congestive heart failure. This arrhythmia in otherwise normal hearts does not appear to be of great hemodynamic consequence.

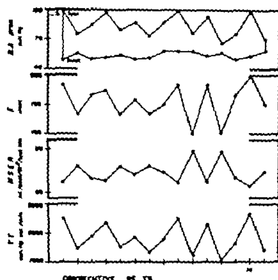


Fig. 21. Consecutive beat-to-beat variation in the brachial arterial systolic (B.A. pres.), ejection time (E.T.), mean systolic ejection rate (M.S.E.R.) and tension-time index (T.T.I.) in one patient with ventricular tachycardia. See Figs. 15 and 16.

Evolutional changes in experimental ventricular tachycardia have been shown to occur in dogs by Wegria and associates.[11,24] They demonstrated that, shortly after the onset of tachycardia, compensatory changes rapidly take place in an attempt to normalize circulatory dynamics. The compensatory mechanism implicated[17] is related to stimulation of the sympathoadrenal system through the activation of the baroreceptors, which promptly respond to a decrease in pulse pressure. As a result of the release of catecholamines, myocardial contractility is increased with an increase in the peripheral resistance, venous return, and eventually cardiac output.

Of interest is the fact that for the same range of heart rate ventricular tachycardia results in a qualitative change in the measured cardiac functions similar to that with atrial tachycardia. The basic difference between the two rhythms appears to be related to the magnitude of the observed changes. The basic physiologic difference between the two rhythms resides in the fact that in ventricular tachycardia the atrial contraction is dissociated from the ventricles, so that this rhythm is basically a form of complete heart block. In addition the sequence of ventricular activation in

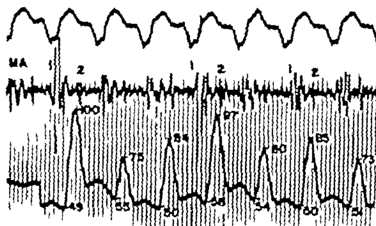


Fig. 22. Brachial arterial pressure curve with the heart sounds recorded at the mitral area (MA) in a patient with ventricular tachycardia. See Fig. 20.

ventricular tachycardia follows an abnormal pathway whereas in atrial tachycardia the sequence of atrial and ventricular contraction occurs in a normal fashion. As a result of the asynchronous atrial and ventricular contractions, patients with ventricular tachycardia have a variable degree of *mitral* and/or tricuspid regurgitation which certainly must contribute to the decrease in cardiac functions seen in this condition. The presence of atrial ventricular dissociation in ventricular tachycardia also explains the beat-to-beat variations in systolic arterial pressure ejection time tension-time *index*, and mean systolic ejection rate (Figs. 21 and 22) The variations in systolic pressures and the changes in the amplitude and character of the heart sounds are useful adjunct signs for the diagnosis of this condition.

The hemodynamic changes described during artificially induced ventricular tachycardia in normal hearts may not be of the same nature and magnitude as the changes observed during spontaneous ventricular tachycardia in diseased hearts. This is primarily related to the fact that homeostatic mechanisms are operating fairly well during the initial phase of ventricular tachycardia, and that they worsen after the paroxysm has lasted for a prolonged period of time

Summary and conclusions

1 Cardiovascular hemodynamics were described in 32 patients with various forms of atrial and ventricular arrhythmias.

2 It was shown that paroxysmal atrial tachycardia resulted in no significant changes in the cardiac output. Artificially induced atrial tachycardia caused a significant rise in the cardiac output, mean systemic pressure tension-time index and stroke power up to a range of rate from 90 to 110 beats per minute Further *increase* in the rate resulted *in* a slight fall in the cardiac output with a significant decrease in the stroke volume peripheral resistance, ejection time, and stroke power

3 Conversion of atrial fibrillation to sinus rhythm *resulted* in no significant changes in the cardiac output at rest During exercise, the cardiac output rose under both circumstances. Stroke volume heart rate, mean systemic arterial pressure peripheral resistance ventricular power and tension time index showed greater changes during exercise in the group with sinus rhythm than in the group with atrial fibrillation

4 Multifocal ventricular premature contractions and ventricular bigeminal rhythm resulted in a significant fall in the cardiac output, stroke volume central blood volume, mean systemic pressure ventricular power and stroke power

5 Spontaneous ventricular tachycardia caused no significant changes in the cardiac output, but a marked decrease in the stroke volume ejection time, and stroke power

6 Patients with complete heart block and slow ventricular rates showed a markedly diminished cardiac output, with an increase *in the* right atrial ventricular and pulmonary arterial pressures and the stroke volume With an increase in the ventricular rate a bell-shaped curve for the cardiac output was observed with a peak response occurring at a rate of stimulation of 62 to 93 beats per minute

7 In patients with complete heart block, properly timed atrial contractions (P R interval of 1 to 300 msec) resulted in a significant rise in the ejection time, mean systolic ejection rate, tension time index, and brachial arterial pressures

8 Thus, it is concluded that in general atrial arrhythmias are of less consequence to the cardiac functions than are ventricular arrhythmias. Atrial systole is important to the cardiac functions in man as long as the atria retain the ability to contract appropriately

We wish to thank Miss Marilyn Hanna, Mrs Mary Vennel, Miss Shirley Cardwell, and Miss Ann Wall for their technical assistance.

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Correlation of renal blood flow determined by the single injection of Hippuran-I^{131} with direct measurements of flow

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Previously[1] we reported on a single-injection technique for measuring the clearance of I^{131} Hippuran.† Good agreement with the classic PAH method performed simultaneously in 8 patients suggested that because of its simplicity and accuracy it might be a useful clinical method for the determination of renal blood flow. I^{131} Hippuran (ortho-iodohippurate) carries its I^{131} label in the natural position in the ring structure, is excreted solely by the kidney, and is a fast diffusing molecule when introduced into the vascular system. Furthermore, Hippuran was one of the first compounds to be used by Homer Smith at the outset of his work on clearance techniques.[2] Many of the compounds which he finally selected for use were compared with Hippuran as his model but, later, other compounds were used because they could be more easily measured than Hippuran.

This study is an extension of our previous work wherein we have calculated renal blood flow using I^{131} Hippuran by both the single-injection technique and classic Fick technique and compared the results with simultaneously measured total renal flow through one kidney of dogs. The literature records surprisingly few instances in which clearance methods have been checked with direct measurements of renal flow. The rationale for using a one-compartment analysis instead of the conventional two is also briefly discussed.

Methods

A. Direct measurement of flow from collection of renal vein drainage. In dogs of 12-23 kilogram weight anesthetized with 32 mg. of morphine and 20-30 mg. per kilogram of pentobarbital, a mid-line abdominal incision was made to expose the kidneys and ureters. Flow was measured from only one kidney, usually the left, since in our hands it was easier to cannulate the left renal vein than the right. The lower end of the left ureter was cannulated with plastic tubing tied into its lumen for accurate measurement of flow of urine

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The arterial supply to the right kidney was identified and the major arteries were ligated completely to exclude this kidney from the circulation. At the conclusion of each experiment the completness of the arterial ligation was verified. In 2 dogs one small arterial branch was still patent since it had not been included in the arterial ligatures. Since the main renal vein in each had been tied also, we believe that very little blood could have flowed into the kidney in these animals. Radioisotope assay of kidney sections in one of these animals proved that only a small amount of activity was present. After this unilateral complete arterial ligation, 100 to 150 mg. of heparin was given and the left common carotid artery was cannulated for measurements of mean blood pressure and for arterial sampling. A polyethylene tube 11 cm. in length and with an internal diameter of 3.76 mm. was inserted into the opened right renal vein and passed across the inferior cava into the left renal vein for 4 or 5 cm. and tied in place. The tube was connected to the cannulated right external jugular vein with a 77-cm. length of polyvinyl tubing (internal diameter of 6.3 mm.). The left ovarian or spermatic vein was tied.

In the distal portion of the tubing close to its return into the external jugular a T tube was inserted for measuring the renal outflow in a graduated cylinder during periods of 10 to 15 seconds. The level of the drainage outlet was adjusted to the pressure in the external flow circuit. Measurements of renal venous flow were made in duplicate immediately before and after each clearance period, but as our techniques improved, 4 to 5 duplicate measurements during the period of clearance were taken. The final flow measurement recorded in the tables represents an average of from 4 to 10 duplicate separate flow determinations in any clearance period.

B. Hippuran clearances as a measure of renal blood flow.

1. SINGLE INJECTION TECHNIQUE. A single intravenous injection of 10 to 50 μc of I^{131} Hippuran in from .5 to 2 ml. volumes was made rapidly. Samples of arterial blood from which the clearances were calculated were drawn at approximately 9, 12, 15, and 18 minutes after the injection of Hippuran. All samples and the standard for dose calibration were pipetted to 2-ml. volumes and counted in an Atomium well scintillation counter. Counts ranged from 2,000 to 8,000 cpm/2 ml. of whole blood. Cpm/ml. of arterial whole blood were plotted on semilog paper as a function of time using the four points from 9 to 18 minutes. From the exponential decay curve calculation of flow was made using the formula $F = m_2V_2$, where F is clear-

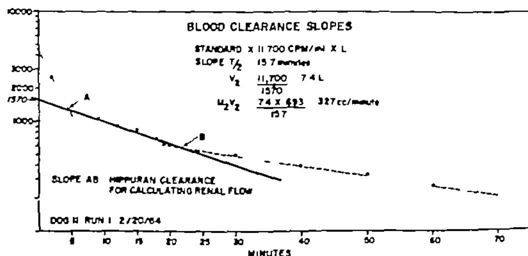


Fig. 1. Typical disappearance curve with blood concentrations plotted from 2 to 70 minutes. The four points at 9, 12, 15, and 18 minutes were used to determine clearance. Note three different exponential slopes. Actual calculation of clearance (flow) has been carried out using line AB.

ance in milliliters, m_2 is the semilogarithmic slope of decline and V_2 is the space or volume of distribution calculated from the injected dose and cpm/ml. in blood at zero time derived from back extrapolation of the slope, AB (Fig 1)

2. FICK PRINCIPLE, $\frac{UV}{B}$ TECHNIQUE. This part of the experiment was performed after the single injection clearance periods had ended From 35 to 100 μc of I^{131} Hippuran was mixed in 250 ml. of 10 per cent dextrose in saline and infused evenly over a period of approximately ½ hour No priming dose was given. Urine was collected in a single period for from 15 to 20 minutes, beginning 10 minutes after start of the infusion Samples of arterial and renal venous blood were drawn simultaneously at the beginning at the middle and at the end of the periods of collection of urine and averaged in the calculations Urine and blood were counted in an Atomium well counter in amounts to give accurate counting statistics.

Results

A Single injection Fig 1 shows a typical time-concentration curve up to 70 minutes. Note the clear semilog decline from approximately 4.5 minutes to 22 minutes after an early rapid period of decline and before the subsequent slower slope up to 1 hour Thus, the curve of disappearance closely resembles that of man[1] and is also similar to that of the rat and rabbit (unpublished data) In the experimental data from which clearances were calculated all points fell regularly except occasionally the point at 18 minutes If this point fell slightly high it was disregarded in drawing the slope and only the first 3 points were used

Table I portrays the measured and calculated flows and some of the data from which each was determined In 11 dogs there were 21 separate runs in which adequate data were available. The average absolute difference between the calculated and the measured flows was 7 6 per cent. Statistical analysis of the actual differences

Table I Results of experiments with single injections

Dog number	Experiment number	Measured flow (c)	Volume*	T½†	Calculated flow (c)	Per cent difference from measured
1	1	340	7 96	13 5	410	+21 0
2	2	272	6 80	17 1	276	+1 5
3	3	220	6 76	21 0	223	+1 4
4	4	260	2 75	6 7	285	+9 6
4	5	197	5 8	21 0	200	+1 5
5	6	148	4 82	29 0	114	−22 3
5	7	131	4 42	22 75	135	+3 1
5	8	94	3 23	23 1	97	+3 2
6	9	275	8 65	25 75	218	−21 5
6	10	215	7 10	21 0	234	+8 9
7	11	179	5 63	21 3	183	+2 2
7	12	160	4 02	17 4	160	0
7	13	158	4 45	18 3	167	+5 7
8	14	212	5 72	18 0	220	+4 2
8	15	240	7 23	20 0	250	+4 2
9	16	[illegible]66	6 8	21 0	225	−13 4
9	17	183	6 96	24 0	200	+9 3
10	18	170	5 16	19 5	179	+3 3
10	19	168	5 45	19 5	193	+14 9
11	20	336	7 45	15 7	327	−2 7
11	21	216	6 73	21 8	214	−0 9
				Average absolute difference:		7 6

*Volume of dilution in liters.
†T/2 of slope in minutes.

showed that they were not significantly different from 0 ($p > .05$). In 3 runs there were differences of +21, +22, and −22 per cent. Sixteen of the 21 determinations, however, agreed within ± 10 per cent.

The range of measured flows for the single kidney varied from a minimum of 94 ml. to a maximum of 340 ml. per minute. In certain of the animals, from 200 to 300 c.c. of blood was removed in order to drop the pressure and change the flow, but usually this was a rather ineffective means of reducing flow markedly without subsequently causing the deterioration of the animal. Therefore, in Dog No. 11 the left main renal artery was isolated and after cannulation was perfused from the left femoral artery. After the first run (Experiment No. 20) a screw clamp was tightened on the renal arterial perfusion tubing to drop the perfusion pressure from 130 to 75 mm. Hg. A second injection was then made and the second run (Experiment No. 21) shows that the reduced measured renal flow is reflected accurately in an almost identical reduction in flow as measured by the Hippuran clearance.

Table II shows the results of 9 experiments in which by large infusions, bleeding, or restriction of arterial inflow, either the blood flow or urine volume was markedly changed. The changes in altered measured flows were usually well reflected in clearance flows, irrespective of wide changes in urine volumes. The reductions in flow were associated with either reduction in calculated spaces of distribution or increases in the slope half times, or with both. In Dog No. 5 the kidneys were small and grossly were diffusely scarred. Microscopic sections revealed severe destruction of renal parenchyma with interstitial fibrosis consistent with a diagnosis of chronic pyelonephritis. During the study of this dog only small amounts of bloody urine were excreted, but the clearance yielded values of flows in good agreement with the direct flow measurement.

B. Fick principle. In 6 of the 11 dogs used in this study, additional measurements of Hippuran clearance, using arterial samples, renal A-V differences, and total urine collection, were made at the completion of the determinations using the single injection technique. From Table III, which gives the essential data from these studies, it can be seen that with this technique the average absolute difference between the measured and calculated flows was 4.0 per cent, with measured renal flow in the ranges of from 114 to 320 ml. per minute. The large A-V differences noted for I[131] Hippuran have been a consistent finding in this preparation

Table II. Results of changes in either blood flow or urine volume in same animal

Dog number	Experiment number	Measured flow (ml./min.)	Clearance flow (ml./min.)	Volume*	Slope T/2 in min.	Urine volume (ml./min.)	Comments
5	7	131	135	4.42	22.75	0.2	B.P. 95 mm. Hg Bled 450 ml.
	8	94	97	3.23	23.1	0.2	B.P. 50 mm. Hg
7	11	179	183	5.63	21.3	2.0	B.P. 125 mm. Hg Bled 400 ml.
	12	160	160	4.02	17.4	1.0	B.P. 85 mm. Hg Reinfused
	13	158	167	4.45	18.5	2.0	B.P. 100 mm. Hg
9	16	266	225	6.8	21.0	0.5	Infusion
	17	183	200	7.0	24.0	1.2	1,000 c.c. 5 per cent dextrose
11	20	336	327	7.4	15.7	0.5	Perfusion pressure 135 mm. Hg
	21	216	214	6.73	21.8	0.1	Perfusion pressure 75 mm. Hg

*Volume of dilution in liters.

Table III Results of experiments with continuous infusions

Experiment number	Measured flow (ml)	Clearance flow (ml /min)	% Difference	Renal A V difference
1	283	312	+10 2	67
2.	281	290	+3 2	36
3.	246	253	+2 9	49
4	173	171	−1 2	31
5	260	275	+6 0	47
6	163	164	0	47

Average absolute difference = 4 0 per cent.

using the single kidney for measurements of flow

Discussion

These results clearly indicate that the clearance values of Hippuran-I[131] determined by both the single injection and Fick techniques accurately reflected the simultaneously measured renal blood flow over a wide range of flow values and under the conditions of changes of flow used in these experiments. The fact that the over all average deviation of the calculated from the measured flows in most instances was less than ± 10 per cent probably attests to the care in technique with which each flow was measured or calculated The agreements by the Fick method were consistently so good in the first 6 runs that further experiments seemed to be unnecessary It should be noted however that renal A V differences of I[131] Hippuran are needed in calculating accurate renal flows, since they are variable and lower than the .85-.92 reported for PAH As the duration of the procedure on any single dog progressed, blood pressures usually fell gradually and the measured flows often fell by 10 per cent during the 20-minute period in which the samples of blood for isotope assays were drawn and while direct flows were measured. These errors were minimized by collecting the renal venous blood for flow measurements during 10-second rather than 15-second periods, and by determining more frequent renal flows during the actual period of the clearance Hence, it is not surprising therefore, that three of the clearance values failed to agree by more than 20 per cent with the measured figures.

Early in the experiments we noticed that urine flows were low often being less than 10 c.c in 20 minutes and that an external probe placed directly on the kidney usually recorded a renogram which showed a prolonged build up period with little or no excretory phase. This indicated that the Hippuran was continuously enter ing the renal parenchyma but leaving it at a less rapid rate Even in this situation the correlations remained good indicating that the so-called build-up and excretory phases of the renogram gave no reflection per se of renal blood flows or blood clear ance of the labeled Hippuran

Most of the previous studies using the single injection technique have treated the removal of sodium iodohippurate by the kidneys by assuming a two-compartment system based on the creatinine clearance model of Sapirstein and associates[3] In this model the concentration curve C is described by the double exponential ex pression

$$C = Ae^{-m_1} + Be^{-m_2} \qquad \text{Eq 1}$$

where A is the intercept of the steep portion of the concentration ordinate and m_1 and m_2 are the disappearance constants or slopes of the semilogarithmic lines.

From this expression the equation for renal flow F in milliliters per minute may be derived as

$$F = \frac{Im_1m_2}{Am_2 + Bm_1} \qquad \text{Eq 2}$$

where I represents the injected dose Thus, in this model it is assumed that the fast component is influenced by the diffusion out of the vascular system into a secondary space, and that the same diffusion constant is present in the reverse direction to delay

the re-entry into the vascular compartment. In addition the boundary condition assumed for the solution is based on instantaneous mixing in the vascular space.

What has seemed to us to represent a more reasonable model is to attribute the early portion of the curve to mixing and dilution phases and to assume, that once equilibrium is reached there is only one single compartment from which the tracer is removed This is similar to the model used by Fozzard[4] in his calculation of renal blood flow from a single injection of Diodrast

Our model[1] predicts the equation

$$F = \frac{Im_2}{B} \qquad \text{Eq } 3$$

where again, I is the injected dose B is the intercept at time zero of the shallow line of the concentration ordinate and m_2 is the semilogarithmic slope of the second phase of the curve

It is seen that Equation 3 closely approximates Equation 2 when the value of Am_2 is appreciably smaller than Bm_1 This condition is suggested by the data of Hine and associates,[5] which show the half times of the two phases to be approximately in the ratio 5 1 and by the data of Mandel and associates,[6] which illustrate this at 10 1

Since the term $\frac{I}{B}$ merely represents the total dilution volume V the expression for renal flow may be calculated by the equation

$$F = Vm_2 \qquad \text{Eq } 4$$

This is similar to the curve analysis used by Stokes and Ter Pogossian [7]

Although the discrepancy between calculations based on the two different models would be no greater than the ratio of Am_2 to Bm_1 what is probably more important are the assumptions that both models imply The single compartment has appeared to us to be more reasonable both from the known effect of the early mixing curve[5] as well as from the constant ratio between the Hippuran concentration in the red cells and in the plasma which is indicative of such rapid exchange that a virtual one-compartment equilibrium may be assumed [9]

Although the two-compartment system postulates equal intercompartmental clearance rates, both into and out of the secondary space we have found that during the first few minutes of the mixing phase a large fraction of the injected material is flowing into the kidney cells for excretion This largely invalidates the use of the early part of the concentration curve in the two-compartment interchange analysis. In addition the two-compartment analysis requires recording for approximately 50 minutes, and the consistency of the disappearance curve of I^{131} Hippuran to a two-phase exponential system beyond 20 minutes has not been established Hine and associates[5] have resolved the curve into four components and in the present investigation deviations from an exponential decay usually have been found after 20 minutes (Fig 1) We believe that this deviation from the earlier exponential decline after 20 minutes is due to a wash out or backflow of Hippuran previously cleared from the blood by the kidney cells into the renal venous circulation. This phenomenon has previously been reported by Kinter and Cline[10] for Diodrast in the fish in vitro and we have demonstrated this washout in our laboratory in both the dog and the rabbit in vivo Although the actual amounts of backflow have yet to be established the effect on the disappearance curve will be greatest when the concentration of Hippuran in the blood is low Then even a small back release of Hippuran will cause an increase in the blood concentration and a retarded decline in the disappearance slope. The physiologic data and a complete description of the model on which these results are calculated will be the subject of a later report

Certain essentials in technique should be mentioned if the single-injection method is to be useful Accurate measurement and injection of the dose of I^{131} Hippuran is mandatory In these experiments, since flow through only one kidney was measured the slopes of clearance were slower than in dogs with both kidneys functioning It was found that the slope of the residual clearance, 20 minutes after injection and for approximately 1 hour declined at a half time of about 30 minutes. Because of this, blood drawn for background determinations in those few runs performed 10

to 15 minutes after the finish of the previous clearance period gave relatively high counting rates. If this high background value were subtracted from each subsequent blood sample of the falling concentration during the clearance period spuriously steep slopes would result and falsely high renal flows would be calculated. To correct for this, a slope with a half time of 30 minutes was plotted on graph paper. From this slope a corrected background for each sample of the clearance period could be calculated for those few experiments repeated within 10 to 15 minutes from the first. In most of the experiments, however by substantially increasing the isotope dose for each succeeding run and by allowing at least 45 minutes between determinations, we avoided this potential background problem and the single preinjection background value was used. Fig 2 shows the slopes and calculations in Dog No 7 in which 3 successive runs were made.

This single-injection method lends itself especially well to clinical situations in which determinations of renal flow are indicated since it requires no collections of urine and can be performed easily and quickly with a minimum of equipment. The short biologic half time of radioactive Hippuran allows for frequent and repeated determinations.

That Hippuran I^{131} is a suitable material for use in calculating flows from clearance values is shown by the good agreement between measured flows and clearance values determined by the usual constant infusion techniques, even though renal A V differences were low in this preparation.

Summary

1 In 21 determinations in 11 dogs, the clearance values of I^{131} labeled Hippuran calculated from the time-concentration curve of arterial blood after a single injection were compared with flows measured simultaneously by collecting the total renal venous drainage from one kidney.

2. The average agreement was 7 6 per cent in a range of flows from 94 to 340 ml per minute and under conditions of altered blood and urine flow rates.

3 The accuracy and simplicity of the method indicates its clinical usefulness in the area of renal blood flow studies.

4 Classic clearance techniques utilizing Hippuran I^{131} also gave excellent agreement with simultaneously measured flow although renal A V differences were large.

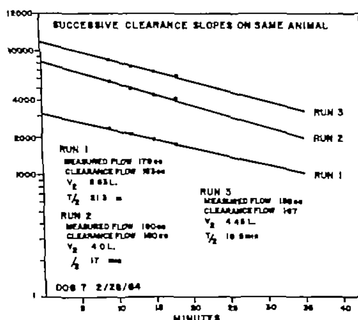


Fig. 2 Slopes and calculations in Dog No. 7 (Table I). Repeated determinations.

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Prinzmetal's variant angina pectoris

Report of a case

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A variant form of angina pectoris with major differences from classic angina of effort was described by Prinzmetal in 1957† and given the descriptive title "angina pectoris inversa In 1960 Prinzmetal and associates[1] reviewed 35 cases of this variant form of angina. There have since been several additional case reports.[2-4]

In this variant form of angina pain occurs at rest, and not with increased physical activity An electrocardiogram recorded during pain shows marked S-T segment elevation in those leads that reflect the ischemic area. With the cessation of pain, the S-T segment rapidly returns to its appearance prior to the onset of the attack.

The case of a patient with this variant form of angina is reported there are several unusual features.

Case report

V H 64-year-old man was admitted to the continuous electrocardiographic monitoring unit with a provisional diagnosis of anteroseptal myocardial infarction. He gave a history of seven separate episodes of retrosternal chest pain during the preceding 4 weeks. Each episode had lasted only minutes nd was not related to exertion rather these episodes had occurred when the patient woke in the morning or while he was relaxing t night. He had continued t his clerical occupation until the day of admission. That morning he experienced severe persistent retrosternal chest pain with radiation to the jaw

On examination the blood pressure was 130/80 mm Hg, and there were no abnormal clinical signs. An electrocardiogram (Fig 1,a) showed left axis deviation, Q waves with S-T segment elevation in Leads V_{1-4}, and deep T-wave inversion in Leads I II and V_{3-4}. Electrocardiographic monitoring was begun, and he was treated with rest in bed. Anticoagulants were not given, since the prothrombin was less than 10 per cent.

Sixteen hours after admission to hospital, severe retrosternal chest pain with radiation to the jaw and left shoulder developed and lasted for several minutes. Coincident with this pain, marked S-T segment elevation occurred. As the pain subsided the S-T segment returned toward the isoelectric line and w than 2 minutes of the cessation of pain the S-T segment and T waves had returned to their appearance prior to the onset of the attack.

Electrocardiographic monitoring was continued for 8 days marked S-T segment elevation was recorded on 56 separate occasions. Chest pain accompanied 48 of these 56 episodes, whereas on eight occasions the typical sequence of electrocardiographic changes was recorded without the patient experiencing any pain, although w ke at these times. There was a constant pattern to the development of the electrocardiographic hanges. The inverted T wave first became upright, then S-T segment elevation occurred and increased in extent, associated with an increase in the amplitude of the R wa Each episode terminated with progressive T-wave inversion and return of the S-T segment toward the isoelectric line (Fig 2). During the period

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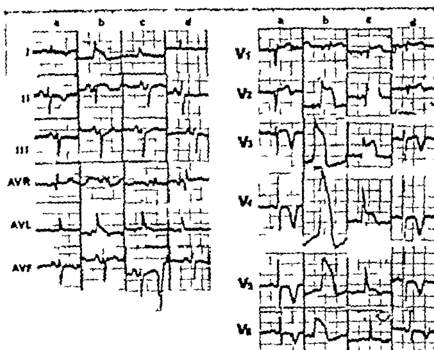


Fig. 1. Twelve-lead electrocardiogram. a, Before pain. b, At height of pain. c, Pain subsiding. d, After pain.

of maximum S-T segment elevation premature ventricular beats were common, often with bigeminy. A standard 12-lead electrocardiogram recorded during an attack showed S-T segment elevation in leads I, II, V, and V (Fig. 1,b,c). By the time of termination of an attack the electrocardiogram had returned to its original appearance (Fig. 1,a,d).

Neither changes in heart rate nor falls in blood pressure were responsible for precipitation of these attacks. Attacks occurred either when the patient was awake or when he was asleep, in which latter case the pain would awake him. Each attack lasted only minutes, occasionally up to 10 minutes. The pain was rapidly relieved by the use of sublingual trinitrin or by the inhalation of amyl nitrite.

The patient was exercised in bed by straight leg raising after almost 3 minutes of exercise chest pain developed accompanied by S-T segment elevation (Fig. 3,b). Pain was relieved within 3 minutes of the cessation of exercise and the administration of 0.3 mg of trinitrin although there was residual S-T segment elevation (Fig. 3,d). Five minutes after trinitrin the electrocardiogram had returned to its original appearance (Fig. 3,a,f).

During the 8 days of electrocardiographic monitoring serum glutamic oxaloacetic transaminase (SGOT) was estimated each 12 hours. Except for two isolated occasions when levels of 41 and 45 units were obtained the SGOT ranged between 17 and 34 units. There was no rise in temperature, the white cell count was 8,000 per cubic millimeter, the erythrocyte sedimentation rate (Westergren) was 63 mm. in 1 hour, serum cholesterol was 220 mg per 100 ml., and the total serum lipids were 900 mg per 100 ml.

Recurrent attacks of chest pain continued until 15 days after his admission to hospital, when a severe attack of retrosternal pain was not relieved by trinitrin. The electrocardiogram then showed changes of anteroseptal infarction with Q waves in Leads V1-4 and the SGOT rose to 96 units. Recovery after infarction was uneventful, there was no recurrence of pain, and the patient has returned to his normal occupation.

Discussion

This patient showed many features of Prinzmetal's variant angina.[1] While he was at rest, recurrent episodes of chest pain occurred, each having the typical distribution of angina pectoris. On all occasions, pain was accompanied by changes in the electrocardiogram consisting of marked S-T segment elevation and an increase in the amplitude of the R wave. At the height of the chest pain and S-T segment change premature ventricular beats were common. Pain was rapidly relieved by trinitrin or amyl nitrite; as the pain subsided, the S-T segment returned toward the isoelectric line. Myocardial infarction occurred in the anatomic site indicated by the electrocardiographic changes during the preceding transient episodes of chest pain. After myocardial infarction the pa-

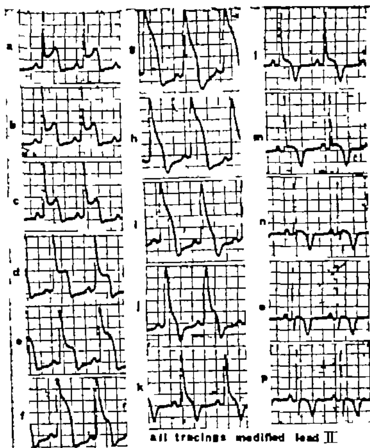


Fig. 2. Electrocardiogram from monitoring lead, showing sequence of changes during transient pain. *a*—*g*, Pain developing. *l*—*m*, Pain subsiding. *n*—*p*, Free of pain.

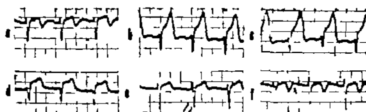


Fig. 3. Exercise electrocardiogram. All tracings are modified Lead II. *a*, Rest. *b*, Pain after 3 minutes of exercise. *c*, Trinitrin, 0.3 mg. sublingually. *d*, No pain 3 minutes after trinitrin. *f*, Five minutes after trinitrin.

tient was free of pain. These features are all described as typical of the variant form of angina pectoris.[1] This patient does, however, illustrate two features not previously reported.

On eight separate occasions while the patient was awake, marked S-T segment elevation was recorded in the absence of chest pain. In each of these episodes the S-T segment elevation was equal in degree to that which occurred with pain. One may conclude from this that the changes occurring within the myocardium leading to S-T segment elevation are not identical to those changes causing pain.

In the reported cases of variant angina, exercise did not produce pain and with exercise tests there was either a normal response to exercise or S-T segment depression occurred unaccompanied by pain.[1-3, 7]

From autopsy evidence Prinzmetal and associates[7] showed that variant angina was due to an almost complete (80 per cent) occlusion of a major coronary artery. They postulated that a transient increase in arterial tone could lead to complete but temporary obstruction of this narrowed major vessel and thus pain with S-T segment elevation. They considered that arterial tone was increased at rest and was decreased on exercise and thus explained pain at rest but not with exercise.

Initially this patient suffered chest pain at rest and not during physical activity. Several days after his admission to hospital, however, exercise resulted in chest pain associated with S-T segment elevation. This pain was relieved rapidly and the electrocardiogram returned to its original appearance with deep T wave inversion after cessation of exercise and administration of trinitrin. Bayley and LaDue[8] showed in dogs that coronary artery occlusion led to increased T wave inversion before S-T segment elevation appeared. They considered that T wave inversion was due to ischemia preceding a more severe degree of ischemia with S-T segment elevation. At rest this patient showed deep symmetrical T wave inversion in Leads I, II, and V_{2-6}; this presumably indicated a severe degree of myocardial ischemia at rest. It is postulated that with exercise the myocardial blood flow was further compromised leading to pain with S-T segment elevation.

A single electrocardiogram recorded during pain in a patient with Prinzmetal's variant angina could lead to an erroneous diagnosis of acute myocardial infarction. Diagnosis is difficult when retrosternal chest pain occurs only at rest; probably variant angina is present in few such cases. As in this patient, and in the case reported by Lunger and Shapiro,[5] continuous electrocardiographic monitoring provides the most direct means for diagnosis of Prinzmetal's variant angina.

Summary

The case of a 64-year-old man with Prinzmetal's variant angina is reported. Recurrent episodes of chest pain at rest were associated with marked but transient S-T segment elevation. At the termination of pain the electrocardiogram returned to its previous appearance. On occasions, marked S-T segment elevation occurred unaccompanied by pain. Exercise resulted in chest pain with S-T segment elevation. Myocardial infarction occurred 15 days after the patient's admission to hospital; there was no more pain after infarction.

Continuous electrocardiographic monitoring provided an effective means for investigation of this patient with anginal pain at rest.

I wish to thank Dr. Margaret Henderson for permission to publish this case and Dr. Graeme Sloman for helpful criticism.

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Clostridial pericarditis diagnosed antemortem

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Purulent pericarditis and its surgical treatment have been known since the time of Galen.[1] As knowledge of this condition increased during the modern era of medicine, it became apparent that staphylococcal pneumococcal and streptococcal organisms were the most common causative agents of bacterial pericarditis. Only 10 to 20 per cent of the cases of purulent pericarditis are diagnosed before the patient's death. The mortality rate in treated patients averages 25 per cent; untreated purulent pericarditis is always fatal.[1]

The following report describes a case of apparently primary pneumopyopericardium caused by a gas-forming organism of the genus Clostridium. The patient survived for 4 months, only to succumb to further clostridial infection.

Case report

A 59-year-old white typewriter mechanic was admitted to San Francisco General Hospital for the third time in October 1963 in confused state of 2 or 3 days duration. He had been admitted to the hospital for the first time in 1947 because of Laennec's cirrhosis with associated ascites and jaundice. He was not seen again until 1956 when he was again hospitalized and a diagnosis of acute alcoholic encephalopathy was made. In December 1960, he was admitted to another local hospital because of confusion and symptoms of alcohol withdrawal. Examination of spinal fluid obtained by lumbar puncture x-ray films of the skull, and an electroencephalogram showed no abnormalities, and the patient was discharged somewhat improved. In 1962, he was readmitted to the same local hospital because of a similar episode of confusion. He was found to be bleeding from the upper gastrointestinal tract, for which he was given 21 units of blood, and to have pneumonia, which necessitated tracheotomy. The source of the gastrointestinal bleeding was never found. One month before the present admission the patient developed clinical symptoms of myocardial infarction but at his own insistence he was treated at home by his private physician. An electrocardiogram taken at that time showed changes compatible with an acute infarction of the anterior wall of the heart and atrial fibrillation. On Oct. 7 1963 the patient was found at home in a confused and disoriented state. He was admitted to San Francisco General Hospital on the same day. Reliable sources confirmed his statement that he had abstained from alcohol for the past year. The patient had known hypertension of 15 years duration; the last recorded blood pressure reading on Aug. 20 1963 was 200/140 mm. Hg.

On physical examination, the patient was disoriented and belligerent. The temperature was 102°F., pulse 100 per minute and irregular respirations 18 per minute and blood pressure 130/80 mm. Hg. Multiple scars resulting from insertion of intravenous catheters on past occasions, were present on all extremities. Scattered wheezes and rhonchi were heard throughout both lung fields. The cardiac apical impulse was 12.5 cm. to the left of the midsternal line in the sixth intercostal space. The heart sounds were of good quality, the second pulmonic sound was normally split and no murmurs were heard. Atrial fibrillation was noted. The liver was palpable 3 fingerbreadths below the right costal margin. No nuchal rigidity, peripheral edema, or focal neurological abnormalities were present. The diagnosis on admission was acute alcoholic encephalopathy, Laennec's cirrhosis, and fever of unknown origin.

The hemoglobin was 15.1 Gm. per 100 ml., and

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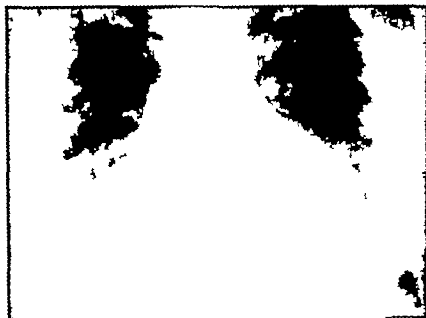


Fig. *1.* X-ray film of the chest on the day of admission, showing enlargement of the heart and haziness of the costophrenic angles. No pericardial air-fluid level is present.

the white cell count was 12,000 per cubic millimeter with 79 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes, and 8 per cent monocytes. The erythrocyte sedimentation rate (Wintrobe) was 30 mm. in 1 hour. The urine specific gravity 1.015 contained a trace of protein; the sediment was normal. The serum sodium was 136, potassium 3.6, chloride 98, and carbon dioxide 5 mEq. per liter. The blood urea nitrogen was 32 mg. and serum creatinine 0 mg. per 100 ml. Serum alkaline phosphatase was 13 Bessey-Lowry units. Prothrombin concentration was 35 per cent. Serum total protein was 6.5 Gm. per 100 ml. with albumin 3.7 and globulin 8 Gm. per 100 ml. Serum total bilirubin was 0 mg. per 100 ml. and cephalin flocculation was 1 plus. Serum lactic dehydrogenase was 112 units and serum glutamic oxaloacetic transaminase was 40 units per milliliter. The antistreptolysin O titer was 50 Todd units. Febrile agglutinins were positive for typhoid O in a 1:20 dilution. On lumbar puncture the initial pressure was 230 and compression pressure 260 mm. Hg. The total protein content of the spinal fluid was 35 mg. per 100 ml., and glucose content was 70 mg. per 100 ml.; no cells were seen. Skin tests for histoplasmosis, coccidioidomycosis, and tuberculosis were negative. X-ray films of the chest showed an enlarged cardiac silhouette possibly due to pericardial effusion (Fig. 1). The electrocardiographic pattern was consistent with atrial fibrillation and an old anterior myocardial infarction.

On the first hospital day a pericardial friction rub was heard over the anterior precordium. On the third day the rectal temperature was 103°F. An x-ray film of the chest showed an air-fluid level, which appeared to be within the pericardial space (Fig. 2A). Pericardiocentesis was attempted but without success. In a subsequent barium-swallow study the proximal esophagus was outlined but the distal esophagus and stomach were not visualized. Several hours later the patient vomited and aspirated barium. A tracheotomy was performed, and penicillin and streptomycin were administered. The following day x-ray films of the chest, decubitus view, confirmed the presence of air in the pericardial space (Fig. 2B). Pericardiocentesis was performed, and 370 ml. of purulent yellow-orange fluid was obtained. Pending the results of laboratory examination of the fluid, chloramphenicol and isonicotinic acid hydrazide were added to the therapeutic regimen. Subsequently the patient's temperature fell to 100°F. Stained smears of the purulent fluid showed many gram-positive rods, which on culture were identified as *Clostridium perfringens*. Despite repeated pericardiocentesis and instillation of aqueous crystalline penicillin, the patient developed signs of pericardial tamponade. On the ninth hospital day a pericardiotomy was performed to relieve the pressure and approximately 200 ml. of purulent material was removed. To ensure continued drainage, a pericardial window was created by suturing the edges of the pericardium to the subcutaneous tissue. Microscopic examination of a specimen of pericardium showed acute and chronic inflammation.

Postoperatively the patient's course was complicated by digitalis toxicity, overhydration, and intractable congestive heart failure. His condition gradually improved and on the tenth postoperative day antibiotics were discontinued. Further examinations, including a Gastrografin-swallow study, esophagoscopy, and a liver scan with radioactive rose bengal failed to demonstrate the source of the Clostridia.



Fig. 2A. X-ray film of the chest taken 3 days after admission showing pericardial air fluid level.

Fig. 2B. X-ray film of the chest, decubitus view taken 4 days after admission, confirming the presence of air in the pericardial sac.

During the second month in the hospital the patient developed bacterial pneumonia for which he was successfully treated by tracheotomy intermittent positive-pressure breathing, and the administration of penicillin. Subsequently he developed slowly progressive peripheral edema associated with gradually increasing venous pressure. During the third month in the hospital, an extensive left pleural effusion occurred, which persisted. The clinical impression of constrictive pericarditis was confirmed by the findings at cardiac catheterization on Dec 30 1963. Pulmonary artery wedge pressure was 19 pulmonary arterial pressure 29/16 right ventricular pressure 33/17 and mean right atrial pressure 20 mm Hg. The right ventricular pressure tracings showed a prominent diastolic dip and a rapid rise to a plateau with a high end-diastolic pressure. The cardiac output was 2.73 liters per minute. A pericardiectomy was scheduled, but a week before the operation was to take place the patient developed a low-grade fever. An x-ray film of the chest showed free air under the di

phragm X-ray films of the abdomen (decubitus and supine positions) taken 1 hour after oral administration of a radiopaque medium (40 per cent Hypaque) showed no free contrast medium in the peritoneal cavity, although free air was again demonstrated. The patient became unresponsive, cyanotic and pulseless and despite attempts at resuscitation he died shortly thereafter.

Autopsy findings. Gross findings at autopsy included the presence of multiple hemangiomas, 1 to [illegible] mm in diameter, scattered throughout the buccal mucosa. The heart weighed 500 grams. The pericardium was 3 mm. thick and adherent. An aneurysm 4 cm. in diameter, which on its medial aspect involved part of the intraventricular septum, was noted at the apex of the left ventricle. An adherent mural thrombus was found on the endocardial surface of the aneurysm. The left anterior descending coronary artery was completely occluded 3.5 cm. from its origin. The ventricular aneurysm was surrounded by a 2- to 3-mm. rim of yellow-gray discolored tissue. A cross section through the interventricular septum revealed a white-gray area of scar tissue that replaced most of the muscle fiber.

The peritoneal cavity held a liter of thin, dark brown fluid containing numerous flecks of fibrinous material. All of the mesothelial surfaces of the peritoneal cavity were inflamed, but no pus or fibrin was present on the surface. The spleen, which weighed 550 grams, was adherent to the splenic flexure of the colon. The splenic artery was divided into two branches; the branch to the inferior pole was completely occluded by an organized thrombus. There was distal infarction of the spleen and surrounding peritoneal inflammation. Numerous hemangiomatous lesions, 2 to 5 mm. in diameter, were found throughout the stomach and small bowel. An old healed ulcer 1.2 cm. in area was seen in the immediate postpyloric region and a duodenal diverticulum was present below the ampulla of [illegible]ter. Multiple pedunculated polyps were scattered over the mucosal surface of the ileocecal region and in the sigmoid colon. No evidence of perforation, erosion of the mucosal surface or other diverticula was seen.

The liver weighed 1,600 grams and was finely nodular. Scarring of the parenchyma was present. The gall bladder contained numerous small soft stones.

Histologic examination of cardiac tissue showed generalized fibrosis. The microscopic findings confirmed the presence of nutritional cirrhosis and hemorrhagic infarction of the spleen. Many areas within the splenic infarct contained clusters of rod-shaped, club-ended organisms. These organisms were also seen in the mural thrombus and adjacent myocardial infarct as well as in the organized thrombus in the lower branch of the splenic artery. Cultures of material from the mural thrombus, spleen, and bile grew *Clostridium perfringens.* Cultures of blood, peritoneal fluid, and cardiac and pericardial tissue showed no growth.

The autopsy findings indicated that the probable immediate cause of death was septic embolism to the spleen with resultant peritonitis and toxic shock.

Discussion

Clostridial infections have been found in almost every site in the body.[1] Clostridial pericarditis has been reported on several occasions in association with war wounds of the thorax[1,2]; however, no well-documented case of spontaneous gas gangrene of the pericardium was found in the English literature. Several cases of pneumopyopericardium of uncertain etiology have been described by Meyer,[3] Rigler,[4] James,[5] and Shackelford.[6] Boyle, Pearce, and Guze[7] found mixed streptococcal and clostridial pericarditis at autopsy in a patient who died 60 hours after an acute myocardial infarction.

The etiological factors in pneumopericardium and pneumopyopericardium have been divided by Meyer[3] into three main classes: (1) trauma, (2) perforation of neighboring organs, and (3) systemic infection or the apparently spontaneous development of fluid, pus, and gas in the pericardium. The pericardial infection in the present case apparently belongs in the latter category. Metastatic gas gangrene, with or without septicemia or an already well-established focus of infection, is extremely rare, particularly in the absence of injured or ischemic tissue elsewhere in the body.[1,7,8] Hallock[9] was the first to report the possible association of septic cardiac infarction with pyopericardium. Boyle and associates[7] also described a case of pyopericardium in a patient with an old cardiac infarction and a ventricular aneurysm at autopsy; the aneurysm was found to contain a fresh myocardial abscess.

Conn[10] recently pointed out that coliform septicemia is not uncommonly found in association with cirrhosis, perhaps because the reticuloendothelial system of the liver is often bypassed in patients with portal hypertension and intrahepatic shunts. Also clostridial organisms are frequently found in the gastrointestinal tract.[1,7,11,12] In the present case, such organisms may have invaded the blood stream initially through a small gastrointestinal lesion that subsequently healed and was not detected at autopsy. The organisms then may have seeded various tissues, including the myocardium, and lain dormant in spore form for some time. It is possible that the myo-

cardial infarction experienced by the patient 1 month before admission provided the proper environment for the propagation of clostridial organisms and their subsequent spread to the pericardium. Once the pericarditis had been established massive doses of penicillin given parenterally and local instillation of penicillin into the pericardial sac failed to eliminate the infection and obviate the need for pericardiotomy. It is of interest that viable organisms were still present in the myocardium mural thrombus, and splenic artery thrombus nearly 4 months after antibiotic therapy.

Summary

This report describes a case of spontaneous gas gangrene of the pericardium in a patient who survived 4 months. The diagnosis was established antemortem and the patient was treated with broad-spectrum antibiotics, injected intramuscularly penicillin, given parenterally and by local instillation, and surgical drainage. He rapidly developed constrictive pericarditis and died probably from septic embolism to the spleen, with subsequent peritonitis and toxic shock, before pericardectomy could be performed. It is postulated that the process arose as a primary infection in a mural thrombus or in an area of ischemic myocardium after clostridial bacteremia.

I am indebted to Dr. Elliot Rapaport, Director Cardiopulmonary Unit, San Francisco General Hospital, for his invaluable guidance in the preparation of this paper.

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Clinical pathologic conference

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Kurt Amplatz M D
James H Moller M D
Kenneth L Jue M D
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DR RAGHIB This male infant was first admitted to the University of Minnesota Hospitals at the age of 2 days The infant's color was poor at birth and cyanosis was noted when he was 12 hours old On admission the infant was cyanotic The pulse rate was 140 and the respiratory rate was 38 each per minute The blood pressure was not measured No cardiac murmurs were present The second cardiac sound was normally split There was no evidence of congestive cardiac failure The electrocardiogram (Fig 1,*a*) was interpreted as showing right atrial enlargement and left ventricular hypertrophy The Schmitt-system vectorcardiogram (Fig 1,*b*) recorded at normal standardization demonstrated that the major portion of the electrical forces was directed posteriorly and to the left which indicated left ventricular hypertrophy for this age The roentgenograms will be interpreted by Dr Amplatz

DR. AMPLATZ The thoracic roentgenograms (Fig 2) show the heart to be slightly enlarged and there seems to be decreased pulmonary vascularity in both pulmonary fields. The apex of the heart is rounded suggesting left ventricular enlargement but the left atrium does not appear to be enlarged The pulmonary arterial segment is not prominent and there is a left aortic arch A forward angiocardiogram will be presented later

DR. MOLLER This infant presents a problem not infrequently seen by the pediatric cardiologist. In the early neonatal period cyanosis was seen and the infant was not in a state of acute respiratory distress or cardiac failure. I think that the most important finding on which to base the differential diagnosis of this case is the thoracic roentgenogram This revealed the pulmonary vascular markings to be diminished On this basis, one can eliminate from consideration a number of cardiac and noncardiac causes of cyanosis in the newborn infant The major diagnostic possibilities in the clinical situation of cyanosis associated with diminished pulmonary vascularity are (1) pulmonary valvular atresia with intact ventricular septum (2) tricuspid atresia with pulmonary stenosis (usually with normally related great vessels) and (3) the tetralogy of Fallot with pulmonary atresia. The electrocardiogram is useful in distinguishing between these three possibilities, and in this case suggests pulmonary valvular atresia. With the axis being normal tricuspid atresia is virtually eliminated from consideration since this malformation is usually associated with left

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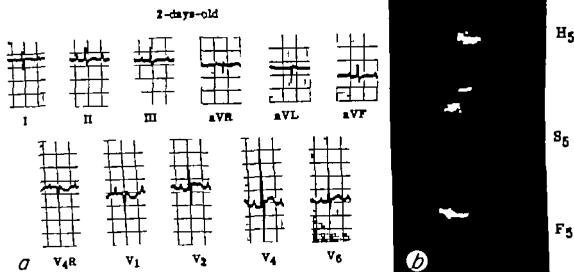


Fig. 1. Electrocardiogram (a) and vectorcardiogram (b) when the patient was 2 days of age. (See text for discussion.)



Fig. 2. Frontal (a) and lateral (b) thoracic roentgenograms when the patient was 2 days of age. (See text for discussion.)

axis deviation. The electrocardiogram was interpreted as indicating left ventricular hypertrophy. In the present clinical situation however the pattern of the precordial leads may indicate an absence of right ventricular electrical forces, as from a minute right ventricle, so that the left ventricular electrical forces are unopposed and present the pattern of left ventricular hypertrophy. Pulmonary valvular atresia with intact ventricular septum or tricuspid atresia may each be associated with such an electrocardiographic pattern in the precordial leads, whereas the tetralogy of Fallot, either with severe pulmonary stenosis or atresia exhibits right ventricular hypertrophy. I think that the primary consideration at this point must have been pulmonary valvular atresia and the next diagnostic procedure was the recording of a forward angiogram,

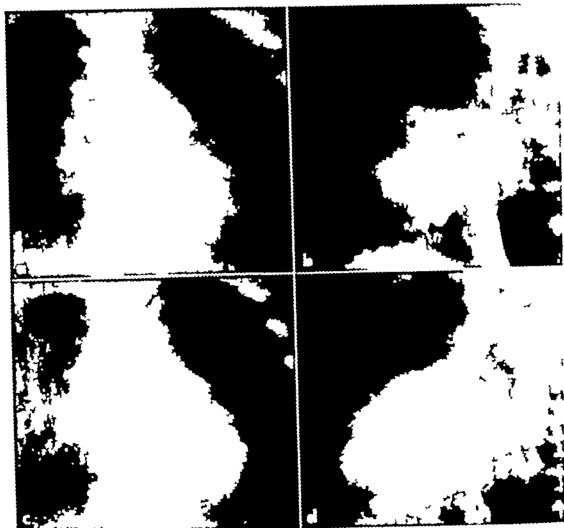


Fig. 3. [illegible] gram when the patient was 2 days old. *a* and *b*, Frontal and lateral projections, respectively, during the [illegible] phase of venous angiography. *c* and *d*, Frontal and lateral projections, respectively, during the [illegible] phase of [illegible] study. (See text for discussion.)

which I wonder whether we may see now please.

DR. AMPLATZ. The forward angiogram (Fig. 3) shows a massive right-to-left shunt at the atrial level as in tricuspid atresia or pulmonary valvular atresia with intact ventricular septum. After opacification of the mildly enlarged left ventricle there is filling of both great vessels which appear to be normally related. The aorta is fairly large and the pulmonary artery is small.

DR. MOLLER. In view of the observations I would consider the diagnosis to be pulmonary valvular atresia with intact ventricular septum. With the hope that the right ventricle is of normal size I should think that pulmonary valvotomy would be indicated and on an emergency basis.

DR. RAGHIB. At operation performed when the patient was 3 days old the pulmonary valve was found to be normal and no definitive procedure was done. The infant made an uneventful recovery from the exploratory operation although cyanosis persisted. He was discharged from the hospital at the age of 3 weeks. During an outpatient visit when the patient was 6 weeks old an electrocardiogram and vectorcardiogram were recorded (Fig. 4). The electrocardiogram again showed right atrial enlargement and left ventricular hypertrophy. The S wave in Lead V₄ was deeper than in the

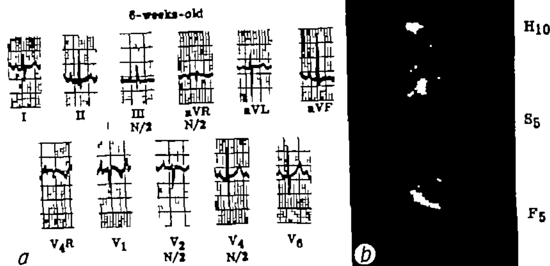


Fig 4 Electrocardiogram (a) and vectorcardiogram (b) when the patient was 6 weeks of age. (See text for discussion.)

first tracing and represents right ventricular forces. The vectorcardiogram with the horizontal plane recorded at half standardization, again shows the prominent electrical forces directed to the left and posteriorly Of note are the terminal forces in the horizontal plane, which are directed to the right and suggest right ventricular hypertrophy in addition to left ventricular hypertrophy

At the age of 2 months the patient was readmitted for further study The physical findings revealed slight cyanosis of the lips. There was a Grade 2/6 high-pitched systolic murmur at the right lower sternal border The second sound in the pulmonary area was diminished Right-sided cardiac catheterization was performed. This revealed a borderline elevation of right ventricular pressure, the systolic pressure being 28 mm Hg and the end-diastolic pressure being 12 mm Hg The pulmonary arterial pressures were 25 mm Hg systolic and 12 mm. Hg diastolic (mean 15) The right atrial pressure was elevated the mean being 15 mm Hg In this chamber the A and "V" waves measured 20 and 12 mm Hg respectively No evidence of a left to-right shunt was obtained Dr Amplatz will describe the cineangiocardiogram obtained at this time.

DR. AMPLATZ A cineangiocardiogram recorded at this time revealed a fairly small densely filled right ventricle that suggested tricuspid stenosis or perhaps primary hypoplasia of the right ventricle. No evidence of a septal defect was obtained

DR. RAGHIB The infant was then discharged and followed in the outpatient cardiac clinic.

The third and final admission to the hospital was when the infant was 3 months old. At this time there was a history of increasing cyanosis, dyspnea, fatigue while eating and inadequate intake of food On this admission the infant was severely ill in a state of congestive cardiac failure. The electrocardiogram gave evidence of hyperkalemia.

The results of laboratory studies were as follows blood urea nitrogen 29 mg per 100 ml of blood The carbon-dioxide content of the blood was 18 mEq per liter In the serum the level of sodium was 139 of potassium 9 4, and of chlorides 100 each in milliequivalents per liter

Treatment included intravenous administration of mannitol insulin glucose, sodium bicarbonate, and calcium chloride. The infant was digitalized After several episodes of cardiac arrest he died 12 hours after being admitted to the hospital

DR. MOLLER I am sure that both the surgeons and clinicians were surprised by the

surgical finding of a normal pulmonary valve. The major consideration after operation must have been tricuspid atresia, despite the electrocardiographic signs contrary to this condition. However, when cardiac catheterization was performed and the catheter was passed into the right ventricle from the right atrium, this possibility was eliminated. The recorded measurements of pressure are interesting in that they revealed that the systolic pressure was only slightly elevated in the right ventricle. The cardiac lesion most frequently associated with a right-to-left shunt with normal

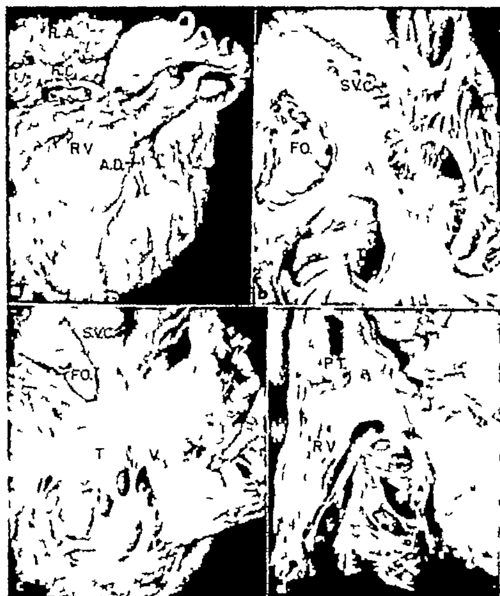


Fig. 5. Specimen of heart. *a*, External view of the heart and great vessels. The vessels are normally related. The right ventricle (*R.V.*) lies farther to the right than the anterior descending (*A.D.*) coronary artery. Above the right coronary artery (*R.C.*) obvious enlargement of the right atrium (*R.A.*) is apparent. *b*, Interior of the right atrium. The superior vena cava (*S.V.C.*) enters in a normal position. The fossa ovalis (*F.O.*) is normally developed, and a valvular-competent patent foramen ovale (*F.O.*) is present. The tricuspid orifice (*T.O.*) is unusually small. *c*, Right atrium and right ventricle. The tricuspid valve (*T.V.*), although normally formed, is small. The right ventricular chamber is small and its endocardium is thickened. *d*, Right ventricle (*R.V.*) and pulmonary trunk (*P.T.*). The right ventricular chamber is small. Its left extent may be seen to the right of the anterior descending coronary artery. The pulmonary valve is normal.

right ventricular pressure is Ebstein's malformation of the tricuspid valve. This condition often is associated with tricuspid insufficiency but such a derangement was not demonstrated by the studies performed. Important findings of the catheterization were (1) elevated right ventricular end-diastolic pressure suggesting diminished ventricular compliance and (2) elevated right atrial pressures, particularly of the "A" wave which suggest tricuspid stenosis. Tricuspid stenosis is an uncommon congenital cardiac malformation either as an isolated lesion or in association with other anomalies. It has been reported to coexist with a ventricular septal defect and with hypoplasia of the right ventricle.

Our attention has been focused upon obstruction to the entry of blood into the right ventricle. The basic cause could be simple tricuspid stenosis. In view of the cineangiographic demonstration of a hypoplastic right ventricle the final clinical opinion must include this condition. In view of the presence of right ventricular hypoplasia our opinion with regard to the tricuspid valve is that it is either intrinsically stenotic or simply hypoplastic along with the right ventricle.

DR. JUE: Pathologically the heart showed normally related great vessels and hypoplasia of the right ventricle and of the tricuspid valve as well as a valvular-competent patent foramen ovale.

From the exterior the great vessels were shown to be normally related and with the aorta wider than the pulmonary trunk (Fig 5,*a*). The latter vessel had an internal diameter of 6 mm whereas the internal diameter of the ascending aorta was 10 mm. The anterior descending coronary artery appeared to pursue a normal course but the right ventricular chamber did not approach the level of this vessel. There was obvious dilatation of the right atrium. Within the cavities of the heart it was apparent that there was a patent foramen ovale of the valvular-competent type and that the tricuspid orifice was markedly reduced in caliber (Fig 5,*b*). Its circumference measured 3.5 cm whereas that of the normal mitral valve measured 5.5 cm.

Leading from the hypoplastic tricuspid orifice was the right ventricle which was also hypoplastic (Fig 5,*c*). This chamber was represented in part by only a small portion of the sinus part of the right ventricle, whereas the major portion of this chamber was formed by the outflow tract. Endocardial thickening of the right ventricle was evident. The right ventricular wall varied in thickness from 2 to 3 mm.



Fig 6 Left side of heart. *a* The left atrium (*LA*) and left ventricle (*LV*) are each enlarged. The arrow shows the path of the channel leading through the valvular-competent patent foramen ovale. The mitral valve is normal. *b* Left ventricle (*LV*) and aorta (*A*). The left ventricular chamber is enlarged. The aortic valve is normal and the ventricular septum is intact.

The pulmonary valve was normal (Fig 5,*d*)

Examination of the left side of the heart showed the pulmonary veins to connect normally with the left atrium The latter chamber was enlarged as was the left ventricle (Fig 6,*a*) The mitral and aortic valves were normal (Fig 6,*b*) The ductus arteriosus was closed In essence this represented an example of hypoplasia of the right ventricle and of the tricuspid valve

DR J.E.T. Dr Edwards would you care to discuss the dynamics in this case.

DR EDWARDS The basic problem in this case appeared to be one of resistance to filling of the right ventricle by virtue of the small size of this chamber The narrow tricuspid valve may not have been a significant abnormality in the presence of the hypoplastic right ventricle since the small tricuspid valve probably simply reflected the basic hypoplasia of the right ventricle (Fig 7) It is assumed on the basis of obstruction to inflow into the right ventricle that a right to-left shunt had occurred through the patent foramen ovale and that

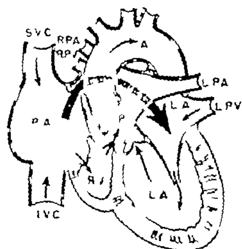


Fig 7 Diagrammatic portrayal of hypoplasia of the right ventricle and of the tricuspid orifice associated with a valvular-competent patent foramen ovale. It is assumed that a transatrial shunt occurred through the foramen ovale on the basis of obstruction to inflow into the right side of the heart. The latter resulted from the hypoplasia of the right ventricle

this shunt accounted for the cyanosis which had been a prominent feature clinically Since there was no communication between the left side of the heart and the pulmonary arterial circulation it is apparent that the volume of pulmonary flow must have been less than systemic flow the latter being composed of that blood which had passed through the lungs in addition to that which had reached the left side of the heart by way of the right to-left transatrial shunt.

The condition presented by the case discussed in this conference is rare The specimen of heart is similar to that in two cases reported in siblings by Medd and associates.[1] In the first of the two cases described in their report tricuspid atresia and pulmonary atresia were two possibilities considered clinically but each of these conditions was excluded during surgical exploration In the second of Medd's two cases, the correct diagnosis was suspected clinically on the basis of a clinical picture similar to that in the first case and knowledge of the pathologic findings in the first sibling

Angiocardiography is the ideal method of distinguishing hypoplasia of the right ventricle with patent valves, on the one hand from tricuspid atresia or pulmonary atresia with intact ventricular septum on the other

Lacking confirmation of a patent pulmonary valve the clinician is faced with the possibility that the pulmonary valve may be atretic In such a circumstance surgical exploration is justified since pulmonary atresia with intact ventricular septum left untreated frequently results in death in the neonatal period Moreover surgical creation of an opening in an atretic pulmonary valve may be a lifesaving measure in those cases in which the right ventricular size is nearly normal

Diagnosis Hypoplasia of right ventricle and of tricuspid valve

REFERENCE

1 Medd W E., Neuf H H N., Weidman W H and Edwards, J E. Isolated hypoplasia of the right ventricle and tricuspid valve in siblings Brit. Heart J 23:25 1961

Left bundle branch block—A clinical assessment Part III*

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Premature contractions in the presence of left bundle branch block

Bisteni and associates[14]† have conducted careful experimental studies concerning the morphology of ectopic beats, both ventricular and supraventricular Their studies represent a valuable contribution, and their findings as they pertain to premature beats in the presence of left bundle branch block will be reviewed at this time. In addition to the experimental studies, they have clinical corollaries.

1 Premature ventricular contraction occurring between the peak of the P wave and the beginning of the QRS in the presence of left bundle branch block with the impulse originating in the left ventricle (*Fig 30*) When the ectopic focus is in the left ventricle, in the presence of left bundle branch block, and occurs between the ascending limb of the P wave and the beginning of the anticipated QRS, the extrasystolic ventricular complex tends to become narrower and less bizarre.

When the ventricular ectopic stimulus arises at a critical moment on the PR segment, a QRS of normal duration and morphology occurs (Fig 30,*a*) Bisteni and associates[14] have explained the normal QRS duration as being due to the fact that a premature beat originating in the left ventricle activates the left ventricle slightly before the right ventricle receives its impulse which comes down the intact right bundle from the sinus node. This results in an essentially normal order of activation with the left ventricle slightly preceding the right ventricle. This sequence of activation counterbalances the effect of the left bundle branch block.

If the ectopic ventricular focus discharges before this critical moment a morphology of incomplete right bundle branch block will be produced (Fig 30,*b*) In other words, this left ventricular premature contraction somewhat precedes the supraventricular activation of the right ventricle and gives the expected morphology of an incomplete right bundle branch block pattern.

If the ventricular stimulus occurs after the critical moment, but before the beginning of the expected QRS complex, the morphology will resemble incomplete left bundle branch block. Here the sequence of activation is as follows the sinus impulse coming down the intact right

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†For the list of references, see Part I of this article in the October issue

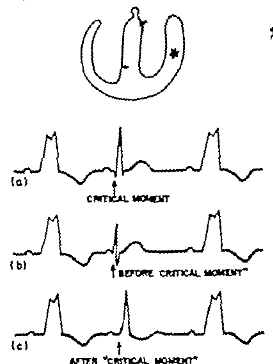


Fig 30 Premature ventricular contraction arising in the left ventricle in the presence of left bundle branch block and occurring between the P wave and the anticipated QRS complex *a* Occurring at the critical moment *b* Occurring before the critical moment *c* occurring after the critical moment. (Adapted from Bisteni and associates.[119])

bundle begins the activation of the right septal mass slightly ahead of the activation of the left ventricle and left septal mass produced by the ectopic left ventricular focus (Fig 30,*c*)

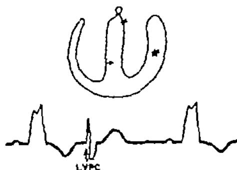
Other explanations have been given for the appearance of a premature ventricular contraction of essentially normal duration occurring in left bundle branch block. Bisteni and associates[119] have suggested that if the ectopic focus arises in the physiologic barrier separating the right septal mass from the left septal mass, the ectopic stimulus reaches both ventricles almost simultaneously and the ventricular morphology of the premature beat tends to become normal Others have suggested that the ectopic focus may be located in the upper portion of the interventricular septum[84] or in the left side of the interventricular septum just below the level of the block.

II Premature ventricular contraction occurring between the end of the T wave and the beginning of the P wave (responsive portion of the cardiac cycle) in the presence of left bundle branch block (Fig 31) When the ectopic focus is in the left ventricle the premature beat has the appearance of a right bundle branch block and there is no difference in its morphology when the premature beat occurs in this part of the cardiac cycle in the presence or absence of left bundle branch block (Fig 31,*A*)

When the premature ectopic focus is located in the right ventricle, the premature ventricular contraction has the appearance of a left bundle branch block, and again there is no difference in the morphology when the ventricular ectopic beat occurs in this part of the cardiac cycle either in the presence or absence of left bundle branch block (Fig *31,B*) It should be noted that the configuration of the premature beat in this instance is similar to that of the QRS complex of supraventricular origin

III Premature ventricular contraction arising between the ascending limb of the P wave and the beginning of the QRS in the presence of left bundle branch block when the ectopic focus is located in the right ventricle (Fig 32) Bisteni and associates[119] have pointed out that in this situation the entire heart is activated by the ectopic stimulus and the possibility of stimuli summation or fusion beats is eliminated The premature ventricular contraction in this situation will resemble in configuration that of the supraventricular QRS complex and has the expected morphology of a right ventricular premature contraction that of a left bundle branch block pattern

IV Supraventricular premature beat occurring between the T wave and the beginning of the P wave in the presence of left bundle branch block (Fig 33) Ordinarily when a supraventricular premature contraction occurs in the presence of left bundle branch block the extrasystolic QRS complex is similar to that of sinus origin (Fig 33,*a*) This is especially true when the premature atrial (or nodal) contraction occurs during the responsive portion of the cardiac cycle between the end of the T wave and the onset of the P wave[84] If however the premature atrial contraction occurs early



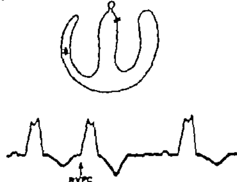


Fig 31 A Premature ventricular contraction arising in the left ventricle in the presence of left bundle branch block and occurring between the T wave and P wave. B Premature ventricular contraction arising in the right ventricle in the presence of left bundle branch block and occurring between the T wave and P wave. (Adapted from Bisteni and associates.[169]) LVPC and RVPC Left and right ventricular premature contractions, respectively

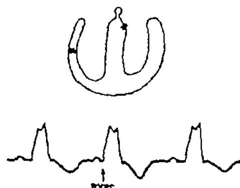


Fig 32 Premature ventricular contraction arising in the right ventricle in the presence of left bundle branch block and occurring between the P wave and the anticipated QRS complex. (Adapted from Bisteni and associates.[169]) RVPC Right ventricular premature contraction.

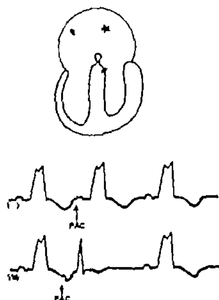


Fig 33 Supraventricular premature contraction in the presence of left bundle branch block occurring between the T wave and P wave a Occurring after the T wave b Occurring before the T wave inscription is completed (Adapted from Bisteni and associates[169]) PAC Premature atrial contraction.

in the diastolic phase of the cardiac cycle, and the stimulus arrives at the ventricles between the peak and the end of the T wave, or the so-called relative refractory period the morphology of the premature beat may either approach or become normal (Fig 33,b) Bisteni and associates[169] have offered the following possible explanation of the mechanism that produces the essentially normal appearing ventricular complex The unblocked right bundle branch is in a relatively refractory state when the ectopic supraventricular stimulus is prematurely discharged following a short diastolic pause that is not sufficient for complete recovery of the right bundle branch These authors postulate that the left bundle continues to transmit impulses, even in the presence of an advanced degree of block. In this situation both the right and the left ventricles have a similar delay and there is less asynchronism of ventricular activation resulting in a QRS complex of essentially normal duration and morphology (Fig 33,b)

Paroxysmal arrhythmias in the presence of left bundle branch block

It is a well-recognized fact that any supraventricular arrhythmia may occur concomitantly with left bundle branch block. Atrial fibrillation, atrial flutter, and supraventricular paroxysmal tachycardia with left bundle branch block are not uncommon. When the ventricular response is rapid and the atrial mechanism is not readily identified, such arrhythmias may be confused with paroxysmal ventricular tachycardia.[illegible] Supraventricular tachycardias or other atrial arrhythmias do not significantly alter the complete left bundle branch block pattern.[94,144]

Less well recognized, however, has been the effect of true ventricular tachycardia occurring in the presence of left bundle branch block. Muller and associates[144] and Bellet[94] have performed some very interesting studies dealing with this problem.

Left ventricular tachycardia in the presence of left bundle branch block. In the presence of left bundle branch block, a ventricular tachycardia produced in the free wall of the left ventricle may show various electrocardiographic patterns, depending upon the automatic center which determines ventricular activity at the particular instant and also on the time of the cardiac cycle in which the ectopic ventricular stimulus falls.[illegible]

LEFT VENTRICULAR TACHYCARDIA WITH THE ECTOPIC FOCUS BEING DISCHARGED IN THE CYCLE BETWEEN THE T AND P WAVES IN THE PRESENCE OF LEFT BUNDLE BRANCH BLOCK. If the ectopic ventricular impulse falls *in the responsive period* of the cardiac cycle between the end of the T and the beginning of the P, a right bundle branch block pattern (left ventricular extrasystolic pattern) is produced (Fig. 31,*A*). If the rate of the ectopic focus is faster than that of the supraventricular focus, the dominant rhythm is left ventricular tachycardia.

LEFT VENTRICULAR TACHYCARDIA WITH THE ECTOPIC FOCUS BEING DISCHARGED BETWEEN THE PEAK OF THE P WAVE AND THE BEGINNING OF THE QRS COMPLEX IN THE PRESENCE OF LEFT BUNDLE BRANCH BLOCK. If the ventricular stimulus occurs within the P-R interval of the cardiac cycle, fusion beats result *with normal or only slightly aberrant* QRS complexes. Muller and associates[144] in their experimental studies demonstrated varying configuration of the QRS complexes in a case of *left ventricular tachycardia* occurring in the presence of supraventricular tachycardia with left bundle branch block. The QRS configuration and duration varied depending on which portion of the P-R *interval the ectopic stimulus from the left* ventricle occurred. If the ectopic beat occurred on or shortly after the P wave, the resulting QRS complex had an incomplete right bundle branch block pattern (Fig. *30,b*). If the ectopic focus occurred slightly later in the P-R interval, the stimulus fused with the activation wave coming from the atrium through the unaffected right bundle branch and resulted in narrowed or relatively normal QRS complexes (Fig. 30,*a*). These workers found that if left ventricular activation occurred immediately after the P wave, Wolff-Parkinson-White-like patterns were produced. Bellet[94] has commented that similar variance in the pattern of ventricular tachycardia has been observed in the human subject, and that some of the instances of narrow QRS complexes observed with ventricular tachycardia may actually be due to such fusion beats.

Right ventricular tachycardia in the presence of left bundle branch block. If the ectopic focus of the paroxysmal ventricular tachycardia occurs in the right ventricle in the presence of left bundle branch block, the resultant QRS morphology is that of a left bundle branch block pattern. This has been demonstrated by Muller and associates[144] to occur *regardless of whether* the ectopic beat is discharged between the peak of the P wave and the beginning of the anticipated QRS complex (Fig. 32) or between the T and the P waves (Fig. *31,B*).

Muller and associates[144] have emphasized that it is of particular interest that a ventricular stimulus which occurs during the P-R interval results in fusion with the supraventricular activation wave and thus produces narrowed or relatively normal QRS complexes. Since the left ventricle below the bundle branch block is activated at almost the same time as the right ventricle, which receives its impulse from

the auricle through the intact right bundle branch the cardiac activation will approach normal limits. The later the ventricular stimulus occurs during the P R interval the closer will the QRS complexes resemble a normal pattern[99,164] These same workers have further emphasized that it is of practical importance to note that complete bundle branch block patterns will be unaltered in supraventricular tachycardias. A decrease in QRS duration during left bundle branch block at the onset of the tachycardia may be the result of a superimposed ventricular tachycardia and presents a serious complication They also emphasized that the correct diagnosis is of great importance in these instances, and that appropriate drug therapy may be life saving

Premature ventricular contractions in the recognition of myocardial infarction in the presence of left bundle branch block

In 1943 Dressler[10] published a case report of left bundle branch block in which a premature ventricular contraction in Lead III showed a QR pattern with a broad Q wave accompanied by S-T segment and T wave changes which were highly suggestive of a myocardial infarction even though the sinus beats with left bundle branch block did not show this pattern In 1945 Simonson and associates[108] published a case of left bundle branch block in which premature ventricular contractions were highly suggestive of myocardial infarction Somerville and Wood[17] also commented on the value of premature ventricular contractions in the presence of left bundle branch block in unmasking myocardial infarction

Bisteni Medrano and Sodi-Pallares[14] reported experimental and clinical studies on the significance of premature ventricular beats in the diagnosis of myocardial infarction They emphasized the similarity of ventricular activation in right ventricular premature beats, supraventricular premature beats with aberrant conduction resembling left bundle branch block, and sinus beats with left bundle branch block. They pointed out that these three conditions can be analyzed in the same manner and that the process of ventricular activation follows a similar sequence, the right ventricle being activated before the left. They further observed that left ventricular premature beats supraventricular premature beats with right bundle branch block aberration and sinus beats with right bundle branch block can be grouped together In these three situations the left ventricle is activated before the right

These workers emphasized that two conditions are necessary for a premature ventricular contraction to be significantly diagnostic of myocardial infarction (1) the unipolar form must be of the QR and not of the QS type since the latter may be found in precordial leads close to or corresponding to the site of origin of the premature ventricular contraction in the ventricle (2) the QR pattern of premature ventricular contractions must be recorded in leads over the epicardial ventricular surface and not over the right or left atrium

These authors further pointed out that the forces generated by the lower third of the left septal mass are not easily identified during normal activation because of the electrical predominance of the forces of the left ventricular free wall and therefore, infarctions in this area cannot be diagnosed in the presence of normal conduction However with a right ventricular premature beat a supraventricular premature beat with some degree of left bundle branch block, or in the presence of sinus rhythm with left bundle block, the activation of the lower portion of the septum becomes relatively dominant and separated as a result of the asynchronous ventricular activation In left bundle branch block, this vector (Vector 2 Fig 4) is oriented toward the left, inferiorly and somewhat posteriorly It is easily recognized as the major portion of the R waves in Leads V_5 and V_6. When an infarction occurs in this region particularly in the anterior portion of the left lower septal mass, this vector is changed and now points more posteriorly and somewhat upward giving rise to Q waves in Leads V_5 and V_6. The recognition of septal infarction in the presence of a supraventricular rhythm with left bundle branch block has already been discussed (see section on the Electrocardiogram in Left Bundle Branch Block with Myocardial Infarction Part II page 699)

Right ventricular premature contraction with left bundle branch block and septal infarction. A right ventricular premature contraction in the presence of left bundle branch block with septal infarction will produce a QR configuration in the left precordial leads similar to the QR configuration in these same leads in the presence of supraventricular conduction and left bundle branch block with septal infarction (*see above*). The right ventricular premature beats in this situation may not supply any information additional to that available in the sinus beats.

Right ventricular premature contraction with left bundle branch block and left ventricular free wall infarction. A right ventricular premature contraction results in initial positivity in the left ventricular cavity, recording an RS complex. Such a right ventricular premature beat in the presence of left bundle branch block with infarction of the left ventricular free wall and in the absence of septal infarction is of no diagnostic help.

Left ventricular premature contraction in the presence of left bundle branch block with septal infarction. A left ventricular premature contraction in uncomplicated left bundle branch block will produce a right bundle branch block configuration with a prominent R wave in the right precordial leads. If septal infarction has occurred, such a left ventricular premature beat may display a diagnostic QR pattern in the right precordial leads even in the presence of left bundle branch block.[144]

Left ventricular premature contraction in the presence of left bundle branch block and free wall infarction of the left ventricle. Lipman and Massie[43] have suggested that, if left bundle branch block is present and is masking an infarction of the free left ventricular wall, a left ventricular premature beat, by changing the sequence of activation, may record a QR complex which is diagnostic of the infarction. It should be emphasized, however, that to be diagnostic of infarction the premature beat must be of the QR and not of the QS type.

It is interesting to speculate that, if the premature contraction arises from the left ventricle and occurs at the "critical moment" between the P wave and the anticipated QRS complex, the QRS configuration may be essentially normal in width. As has already been discussed, this may result from the critical timing of the premature beat originating in the left ventricle, preceding by a slight interval the activation of the right septal mass and right ventricle, resulting in a QRS of essentially normal configuration and duration. In this particular setting an infarction of the free left ventricular wall might well be unmasked by this fortuitous premature ventricular contraction.

A word of caution should be introduced at this time about the injudicious interpretation of premature ventricular contractions in the presence of left bundle branch block. Myers[143] has emphasized that errors may result from attempts to draw diagnostic inferences from the registration of deep Q waves and/or cove-negative T waves in premature ventricular beats, in ventricular tachycardia, and in premature atrial beats with aberrant conduction. He emphasized that an impulse originating from an ectopic ventricular focus directly beneath a precordial electrode may give rise to a QS or QR complex, an elevated RS-T segment, and an inverted T wave, irrespective of the presence or absence of myocardial infarction.

Transient left bundle branch block

Bauer[146] has recently reported 12 cases of transient left bundle branch block and has reviewed the literature. He defined transient bundle branch block as an intraventricular conduction defect that subsequently returns, if only temporarily, to normal conduction.

The first case of transient bundle branch block was reported by Lewis[147] in 1913. In 1932, Morris and McGuire[148] described the occurrence of transient complete left bundle branch block in 2 patients without previously known cardiac disease. In one case the appearance of left bundle branch block was associated with acute pulmonary edema. This patient later developed permanent complete left bundle branch block.[31] In 1938, Comeau, Hamilton, and White[149] found 58 cases in the literature of what they termed "paroxysmal bundle branch block" and added an additional 13 cases of their own. They concluded that paroxys-

mal bundle branch block was to be considered as evidence of the presence of organic heart disease.

Bauer[164] found that the underlying pathology of transient left bundle branch block in his series was related in all but one case to ischemic heart disease. That one patient had aortic stenosis. During periods of normal conduction the electrocardiogram was normal in 3 patients, showed left ventricular hypertrophy in 2, revealed evidence of myocardial ischemia and left ventricular hypertrophy in 3 and showed a pattern diagnostic of myocardial infarction in 4. He emphasized the importance of periods of normal conduction in transient left bundle branch block in unmasking myocardial infarction.

One of his patients maintained normal conduction for over 4 years after transient left bundle branch block. A second patient showed normal QRS complexes for over 5 years, but at the time of his report had again relapsed into an unstable form of left bundle branch block. He cited the case of another patient who returned to normal QRS complexes after 6 years of left bundle branch block.

Bauer[164] reviewed the various etiological factors in transient bundle branch block and emphasized that in his series, as well as in the literature, the condition is most commonly associated with ischemic heart disease accompanied by hypertension. Other less frequent causes are rheumatic heart disease, acute infections, thyrotoxicosis, drugs (including quinidine procaine amide, and potassium) and psychological stress, especially anxiety. He emphasized that the mechanism of transient bundle branch block is obscure. Transient left bundle branch block is often a forerunner of a permanent conduction defect, but the prognosis is perhaps better than that of permanent left bundle branch block.[164]

Transient left bundle branch block may occur during acute myocardial infarction episodes of coronary insufficiency or bouts of left ventricular failure. Bauer[164] observed, however, that the appearance and disappearance of left bundle branch block was often unaccompanied by any recognizable change in the patient's physical condition.

Intermittent left bundle branch block

Intermittent left bundle branch block is to be distinguished from transient left bundle branch block.[12,13] Intermittent left bundle branch block is defined as an unstable form of intraventricular conduction defect in which complexes showing left bundle branch block and complexes showing normal conduction occur in a single electrocardiographic record.[12,13,164] In contrast to intermittent bundle branch block, the entity of transient bundle branch block is a condition in which the conduction defect subsequently returns (if only temporarily) after hours, days, months or years to normal intraventricular conduction.[164]

Bauer[13] has observed 8 cases of intermittent left bundle branch block, and in all the patients had underlying ischemic and/or hypertensive heart disease. One additional case has been reported by Bauer[170] that of a patient with left bundle branch block alternating with the Wolff-Parkinson-White syndrome.

Intermittent left bundle branch block may appear allorhythmically.[12] In analogy to A-V block, such cases may be designated 2:1, 3:1, etc. partial (or intermittent) left bundle branch block.[12] Cutts and Roberts[171] reported a case of 2:1 and 3:1 left bundle branch block in the presence of auricular flutter.

Alternating or 2:1 left bundle branch block. Littmann[172] commented that alternating or 2:1 bundle branch block is an exceptional mechanism which, however, may occur at some time in patients who later develop permanent bundle branch block. This type of alternation is seen almost exclusively with disease of the left bundle branch. It is thought to be the result of incomplete recovery of the left bundle during diastole and occurs at critical heart rates and can proceed to complete left bundle branch block of all complexes at higher rates. The alternate beats may show an incomplete left bundle branch block or completely normal conduction.

Simulated 2:1 left bundle branch block. Schamroth and Chesler[173] reported a case which simulated 2:1 left bundle branch block. The electrocardiogram showed a basic pattern of left bundle branch block

with alternate complexes becoming progressively more normal giving the appearance of 2:1 left bundle branch block. Critical analysis of the tracings by the authors revealed that it was a case of left bundle branch block with end-diastolic ventricular premature beats occurring in bigeminal rhythm resulting in fusion complexes that normalized the bundle branch block pattern and simulated 2:1 left bundle branch block. This then is an example of the type of premature ventricular contractions described by Bisteni and associates[118] which occur in the interval between the peak of the T wave and the beginning of the anticipated QRS complex with the focus in the left ventricle (Fig. 30,a).

Mechanisms in the production and elimination of transient and intermittent left bundle branch block

Bauer[3, 74, 175] has emphasized that bundle branch block can no longer be regarded as a static condition always associated with an organic lesion interrupting one of the main bundle branches. Bauer[175] has reported 5 cases of left bundle branch block under voluntary control in which normal conduction could be induced by a variety of maneuvers including deep inspiration, carotid sinus stimulation and pharmacologic agents. Four of these 5 cases had a critical heart rate above which left bundle branch block appeared and below which normal conduction returned. Bauer has reviewed the various factors which are known to result in the appearance or disappearance of bundle branch block. In most cases of unstable bundle branch block, slowing of the heart rate may result in normal conduction. The various factors that will result in a slowing of the heart rate include deep inspiration, carotid sinus massage, the recumbent posture, and such pharmacologic agents as ergotamine tartrate, amyl nitrite, reserpine, calcium gluconate, and molar sodium lactate.[3] An increase in the heart rate may lead to the reappearance of bundle branch block. Such maneuvers as exercise, assumption of the upright posture, and the Valsalva maneuver have often been shown to precipitate bundle branch block. Drugs such as quinidine, atropine, potassium, procaine amide, and amyl nitrite may produce bundle branch block. Some of these agents produce the conduction defect by depressing intraventricular conduction.

It should be noted at this time that quinidine, procaine amide, and potassium (especially in toxic doses) may result in QRS prolongation which can resemble left bundle branch block. The mechanism of prolongation, however, is thought to be due to diffuse intraventricular slowing.[22,23] In the case of quinidine and procaine amide, the site of delay has been shown experimentally to be in the Purkinje fibers, the myocardial fibers, and at the Purkinje myocardial junction.[24]

In some instances, however, such drugs can precipitate a pattern of conventional complete left bundle branch block.[22,23,24] This is thought to be due to selective depression of conduction in the left bundle.[22] Some of these cases may well have pre-existing subthreshold left bundle branch disease.

In many of the reported cases of unstable left bundle branch block there is a critical heart rate above which the bundle branch block appears. Of interest are those infrequent cases in which the heart rate appears to have a paradoxical effect. In 1959 Dressler[174] reported a case of transient left bundle branch block which occurred during slowing of the heart rate. In 1961 Wallace and Laszlo[177] reported a case in which forceful carotid sinus pressure produced bradycardia and left bundle branch block. In 1963 Vesell and Lowen[176] discussed the rare phenomenon of bundle branch block occurring upon cardiac slowing at a critical slow rate and added a case of left bundle branch block that occurred when the ventricular rate was between 31 and 33 beats per minute. These authors reviewed the possible explanation for this phenomenon and postulated that the appearance of bundle branch block at the slow rate might be due to coronary artery disease with decreased coronary blood flow. They also suggested the possibility of vagal effects, concealed conduction, and automerous conduction as other factors that might produce bundle branch block when there was cardiac slowing.

Wallace and Laszlo[177] have intensively studied their patient with intermittent

left bundle branch block. They found that a variety of physiologic maneuvers including exercise, release of arterial occlusive cuffs, and gentle carotid sinus pressure, would cause this patient's electrocardiogram to change from normal conduction to left bundle branch block. The Valsalva maneuver, the Müller maneuver, and the inhalation of 10 per cent oxygen and of 10 per cent carbon dioxide had no effect on the normal conduction in this patient. As noted before, vigorous carotid sinus pressure in this patient caused a marked slowing of the heart to a rate of 45 to 60 beats per minute and resulted in the appearance of left bundle branch block. It is of interest in their case that although the Valsalva maneuver resulted in an increase in heart rate of from 10 to 30 beats per minute, normal intraventricular conduction was maintained. However, upon release of the Valsalva maneuver, normal conduction converted to left bundle branch block within a few beats on several occasions.

These same authors[177] studied the effect of various pharmacologic agents. They found that intravenous Pronestyl and intravenous potassium produced left bundle branch block, whereas intravenous calcium gluconate and intravenous molar sodium lactate converted the pattern of left bundle branch block to one of normal conduction. The inhalation of amyl nitrite caused the electrocardiogram to change from normal to left bundle branch block. They pointed out that those pharmacologic agents known to depress intraventricular conduction, such as Pronestyl and potassium, induced left bundle branch block. These workers found that the drugs which are known to facilitate intraventricular conduction, such as calcium and molar sodium lactate, reversed the effects of Pronestyl and potassium and converted left bundle branch block to normal conduction. They commented that these responses suggested that the diseased bundle may have been sensitive to influences which primarily affected conductivity.

The observations made by Wallace and Laurdo[177] on their patient during exercise, pharmacologically induced tachycardia, and carotid sinus pressure illustrate that both bundle branch block and normal intraventricular conduction may occur at slow and rapid heart rates. They found normal conduction recorded at heart rates of from 58 to 17? per minute, whereas left bundle branch block was recorded on other occasions at heart rates of from 45 to 160 per minute. It was the opinion of these authors that this wide overlap eliminated heart rate per se as the primary determinant of the type of intraventricular conduction in this patient. They found that carotid sinus pressure both terminated and induced left bundle branch block. Moreover, they found that the form of the ventricular complex (normal or left bundle branch block) during carotid sinus pressure was related to the degree of prolongation of the R-R interval. They suggested that hemodynamic factors may play a major role in determining the form of the ventricular complex. They could not determine from their data whether the response to increased vagal tone was due to direct inhibitory effect of the vagus or to the other factors, such as marked fall in mean arterial blood pressure.

Bauer,[174] in commenting on the underlying mechanism of transient bundle branch block, cited the observation of Carter and Dieuaide[179] that a few intact fibers of the conducting bundle might carry on the normal excitation process under favorable conditions. However, with the appearance of a local circulatory deficiency, failure of the surviving fibers to conduct might occur and precipitate the conduction defect. It is likely that transient bundle branch block may be at least partly a functional or neurogenic disturbance.[17]

Development of left bundle branch block

Bauer[173] has reported personal observations on the development of left bundle branch block in 15 patients. Thirteen of these patients had ischemic heart disease, which was complicated in 10 by hypertension. One patient also had rheumatic heart disease with mitral incompetence and 2 had aortic stenosis. The electrocardiogram was abnormal in all but 2 patients prior to the development of bundle branch block. In 7 there was pre-existing evidence of myocardial ischemia and/or myocardial infarction.

The most common precipitating factor was progressive cardiac decompensation with attacks of left heart failure and pulmonary edema. In patients with ischemic and hypertensive heart disease the occurrence or development of left bundle branch block was usually associated with marked cardiomegaly, triple cardiac rhythm, pulsus alternans, and low output failure. In 2 patients left bundle branch block developed silently without change in the patient's clinical condition. Bauer[178] observed that when bundle branch block accompanies chronic progressive heart failure with increasing cardiac size and recurrent pulmonary edema the appearance of bundle branch block is an ominous sign. All 7 patients in this group died during the period of observation. Minor ischemic episodes presumably resulting in small foci of myocardial infarction or myocardial fibrosis were associated with the development of left bundle branch block in 3 patients. In 2 patients left bundle branch block complicated fatal massive myocardial infarction.

Julian and associates[149] and Bauer[178] found that bundle branch block occurred as a complication in 13 per cent of patients with acute myocardial infarction studied with continuous electrocardiographic monitoring. The majority of these patients died during the acute attack and in the survivors the conduction defect was usually transient. This experience is in contrast to other reports.[19] James[149] commented that bundle branch block is not a clinical problem during acute myocardial infarction. Bauer[178] emphasized that chronic or permanent left bundle branch block is seen infrequently after a typical attack of myocardial infarction with recovery.

Bauer[178] has postulated at least three mechanisms by which bundle branch block patterns may be produced: (1) anatomic severance of the conducting bundle, (2) ventricular hypertrophy and ischemia, (3) functional and neurogenic depression with or without underlying pathologic lesions in the conducting tissue. Left bundle branch block most commonly occurs in patients with ischemic heart disease and hypertension and it is the combination of the two which most consistently leads to the development of this conduction defect. Bauer[178] observed that left bundle branch block generally occurs in ischemic heart disease alone only in the presence of considerable cardiac enlargement and chronic heart failure. In the case of hypertension left bundle branch block is relatively rare unless the hypertension is complicated by inadequate coronary blood supply to the enlarged left ventricle. It is the co-existence of coronary artery disease and hypertension that provides the usual background for pathologic changes leading to left ventricular conduction defects. In such cases left bundle branch block usually follows the onset of chronic congestive heart failure and is of serious prognostic significance.

It was further emphasized by Bauer[178] that even under these circumstances the outlook is not so gloomy as it is often suggested. In his own series, nearly 75 per cent of the patients were alive 3 years after the recognition of left bundle branch block and half were alive after 5 years. He pointed out that the prognosis of bundle branch block appears to be related not only to the type of conduction defect and to the underlying cardiac condition but also to the precipitating factors and mode of onset of the intraventricular conduction disturbance.

The author has followed for several years one patient with mild coronary insufficiency who recently has silently developed complete left bundle branch block with no change in her clinical condition. Another patient with established incomplete left bundle branch block has been followed for several years. Recently he too has silently developed complete left bundle branch block without any clinical episode. His current electrocardiogram and vectorcardiogram are illustrated in Fig. 9 and his apex cardiogram in Fig. 21.

Carotid sinus pressure in the presence of left bundle branch block

Bellet[94] has summarized the effect of carotid sinus pressure in the presence of bundle branch block. (1) There may be no effect. (2) With slowing of the heart rate normal intraventricular conduction may be transiently restored. (This has already been discussed in the section dealing with the mechanisms of transient and inter

mittent bundle branch block.) Bundle branch block may occasionally be abolished with carotid sinus pressure, without a change in rate. (3) Occasionally complete heart block may result from a transient block in the unaffected bundle. (4) Ventricular fibrillation may occur.

Bellet[14] emphasized the case of one patient in whom carotid sinus pressure in the presence of left bundle branch block resulted in irreversible ventricular fibrillation and death. He[14] further observed that in the presence of bundle branch block, vagal stimulation may inhibit conduction in the other bundle, resulting in complete atrioventricular block. If the idioventricular pacemaker does not take over ventricular fibrillation or cardiac arrest may follow. In addition he pointed out that cerebral anoxia may increase the amount of circulating catecholamines which will have a deleterious effect on the heart. He believes that carotid sinus stimulation should be employed with extreme care in the presence of bundle branch block and advanced coronary artery disease.

Discussing the effect of carotid sinus pressure in the presence of left bundle branch block, Bellet[14] observed that with a change from left bundle branch block to normal intraventricular conduction there is an increase in the intensity of the first heart sound. In left bundle branch block the first heart sound is diminished in intensity according to Bellet,[14] because of the lengthening of the interval between the atrial and left ventricular contractions. With return to a normal interval the first heart sound increases in intensity.

Left ventricular hypertrophy and left bundle branch block

The electrocardiogram in left ventricular hypertrophy and left bundle branch block. Wilson and associates[49] noted that, occasionally left ventricular hypertrophy would result in QRS prolongation of even 0.12 sec. When the QRS prolongation in left ventricular hypertrophy reaches 0.12 sec., it may at times be difficult to distinguish this pattern from that of left bundle branch block. Usually in uncomplicated left ventricular hypertrophy there are septal Q waves in the left precordial leads and Q waves in Lead I and the voltage is usually correspondingly high and the R waves are not slurred or bifid in the left precordial leads or in Lead I. The onset of the intrinsicoid deflection in the left precordial leads in uncomplicated left ventricular hypertrophy has been stated to range from 0.05 to 0.07 sec. whereas in left bundle branch block the onset of the intrinsicoid deflection usually is 0.08 sec. or greater.

The New York Heart Association[14] has commented on this problem. It is fairly certain that hypertrophy of the left ventricle can of itself occasionally cause a QRS interval of 0.12 sec. or more. These records will differ from the usual ones due to left bundle branch block in that Q waves will be present in lead I and in the leads from the left arm and the left side of the precordium and the QRS deflections of the bipolar extremity leads usually will be quite high and relatively free from notching and slurring.

Not infrequently the pattern of left ventricular hypertrophy and incomplete left bundle branch block coexist with tall R waves over the left precordium and absence of initial Q waves and slurring of the early portion of the upstroke. Electrocardiograms with these features may be difficult to distinguish from those of complete left bundle branch block. Rasmussen and Moe[49] have suggested that the left ventricular hypertrophy curve and the left bundle branch block curve represent different degrees of retarded conduction to the left heart and that no sharp distinction between them is necessary. These workers also suggested that the electrocardiographic pattern of left bundle branch block is five times more often due to enlargement of the left heart than to a local lesion of the left bundle branch.

Wallace and associates[14] have shown in vectorcardiographic studies of left ventricular hypertrophy that many of the features of incomplete left bundle branch block are present. In incomplete left bundle branch block and in left ventricular hypertrophy the rotation of the QRS loop in the horizontal plane is in the counterclockwise direction.[14, 26] In contrast, in conventional complete left bundle branch block the rotation of the major portion

of the QRS loop in the horizontal plane is in the clockwise direction.

Cabrera and associates[64,114] found that the Lewis index and the magnitude of ÂQRS were helpful in detecting cases of left ventricular hypertrophy in the presence of complete left bundle branch block. They studied 35 cases of complete left bundle branch block and found that when the index of Lewis was above +18 mm. and the magnitude of ÂQRS was more than 20 Ashman units these alterations corresponded to left ventricular overloading due to arterial hypertension or aortic insufficiency. This was found to occur in 60 per cent of their cases.[114] If the index of Lewis was under +18 mm. and the ÂQRS was less than 20 Ashman units, such cases usually corresponded to a disease which did not overload the left ventricle such as coronary sclerosis. However, they did find that in an occasional case with a low index of Lewis there was left ventricular overloading. They concluded that a high index of Lewis strongly suggested left ventricular overloading in the presence of left bundle branch block, whereas a low index of Lewis was of little value in accurate differentiation.[64]

Pantridge[62] studied the electrocardiograms in 109 patients with left bundle branch block. He determined cardiac size by radiologic examination and correlated this with limb lead and precordial voltage criteria for left ventricular hypertrophy. He concluded that left bundle branch block did not obscure the evidence of left ventricular enlargement in the precordial electrocardiogram.

Scott and Norris[17] evaluated the accuracy of electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in the presence of complete left bundle branch block in an electrocardiographic pathologic correlation study. Twenty-nine cases of complete left bundle branch block with autopsy control and without infarction were studied. 13 of these cases had coronary artery disease, 14 had hypertensive heart disease, and 2 were of miscellaneous etiology. The electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in these cases included the determination of (1) high voltage by conventional criteria, (2) index of Lewis, (3) magnitude of ÂQRS. Other electrocardiographic measurements included the determination of the ventricular gradient and the direction, magnitude, and angle between the initial and terminal 0.04 sec. vectors. At autopsy, all 29 cases of complete left bundle branch block demonstrated left ventricular or biventricular hypertrophy. Only 17 of the 29 cases satisfied conventional electrocardiographic criteria for left ventricular hypertrophy. Six of the 29 cases satisfied Grant's criteria of a wide angle (> 110 degrees) between the initial and terminal vectors for anterolateral peri-infarction block with QRS prolongation.[69] However, no infarction or characteristic localization of fibrosis to the anterolateral wall was found in these cases. Nine cases, all with considerable ventricular hypertrophy but without anatomic infarction, exhibited Q waves in Leads I, aVL, V_5, and V_6. Only 4 of these 9 cases satisfied Grant's criteria for anterolateral peri-infarction block.

Electrocardiographic criteria for the diagnosis of left ventricular hypertrophy were thus found by Scott and Norris[17] to be fulfilled in only 60 per cent of cases of complete left bundle branch block, although all 29 cases had anatomic left ventricular hypertrophy. On the basis of this study it was concluded that the majority of patients with the pattern of complete left bundle branch block have anatomic left ventricular hypertrophy, but that this diagnosis can be made in many only by inference. The current electrocardiographic criteria for the diagnosis of left ventricular hypertrophy were found to be unreliable in the presence of complete left bundle branch block, there being a high incidence of false negative diagnoses.

The vectorcardiogram in left bundle branch block with left ventricular hypertrophy. DelPasquale and Burch[117] and Pantridge and associates[1,1] have described the vectorcardiogram in cases of left bundle branch block and left ventricular hypertrophy. The vectorcardiographic loops resembled those of some patients with severe left ventricular hypertrophy. The QRSsÊ loop was oriented to the left, superiorly and posteriorly and rotated in a counterclockwise direction in the frontal plane. The loop had a wide ellipsoid configuration

encompassing a large area and displayed little or no distortion

Left bundle branch block and diffuse myocardial disease

Burch and associates[19] described an electrocardiographic and spatial vector cardiographic pattern associated with diffuse myocardial damage and ventricular aneurysm The electrocardiographic pattern consisted of QRS prolongation with predominantly upright complexes in Leads I V_5 and V_6 but differed from the classic pattern of left bundle branch block in that there was a brief initial upward deflection followed by a shallow downward deflection, and then a prominent prolonged R in one or more of these three leads The vectorcardiogram displayed a slurred narrow distorted QRSsÊ loop oriented superiorly slightly posteriorly and to the left, but always partly to the right of the isopotential point when viewed in the frontal plane. The rotational direction was not uniform but in all cases the vectorcardiogram suggested infarction of the lateral free left ventricular wall either by an arc like deformity with concavity directed to the right or a rapid straight upstroke. The early rightward displacement of the QRSsÊ loop corresponded to the early downward deflection in Leads I V_5 and V_6 and suggested either septal infarction in the presence of left bundle branch block or infarction of the lateral wall of the left ventricle with associated conduction disturbance.

These authors also suggested that the initial leftward spread of depolarization could be due to loss of an initial normal rightward activation in the interventricular septum because of defects in conduction in the left bundle or disease or loss of muscle in the left septum After the initial leftward activation the mean activation to the right beyond the expected time for the normal septal Q wave might be due to associated damage to the lateral wall These authors found this distinctive electrocardiographic pattern in 13 of 24 patients with diffuse myocardial damage, infarction, and ventricular aneurysm

In a subsequent article, Burch and De Pasquale[8] reported a study of the vectorcardiograms of 9 patients with left bundle branch block who at autopsy showed diffuse myocardial disease One had myocarditis and 8 had several large infarcts with diffusely scattered scars. In addition they studied 5 patients with left bundle branch block who had diffuse myocardial disease as the result of rheumatic or idiopathic myocarditis. In all the vectorcardiogram showed what they believed to be a rather characteristic pattern the most outstanding feature being the narrow and distorted QRSsÊ loop oriented superiorly posteriorly and to the left

Left bundle branch block and the Wolff-Parkinson-White syndrome

The combination of left bundle branch block and the Wolff Parkinson-White (ventricular pre-excitation) syndrome is a rare entity Pick and Fisch[18] have reported 2 cases. These workers pointed out that the recognition of this twofold disorder of ventricular activation is possible if pre excitation takes place in the chamber with the intact bundle branch (right ventricle) Pre-excitation may obscure the electrocardiographic pattern of left bundle branch block if the left ventricle is activated prematurely When pre-excitation starts simultaneously in both ventricles, electrocardiographic evidence of left bundle branch block may be obscured by depression of conduction in the normal atrioventricular pathways.

Castellanos and associates[20] have recently reported 2 additional cases and have presented vectorcardiographic as well as electrocardiographic criteria for the recognition of this combination

In 1963 Lev Sodi Pallares and Friedland[21] reported a case of Wolff Parkinson-White syndrome with incomplete left bundle branch block in which the conduction system and the atrioventricular junctions were extensively studied histologically In this case, a communication outside the conduction system was found between the right atrium and the right ventricle. A communication between the junction of the A V node and the bundle and the right atrium was also present but was thought not to be related to the Wolff Parkinson White syndrome. The incomplete left bundle branch block in this case was correlated with atrophy but not com-

plete destruction of the left bundle branch. This was caused by an old septal infarct which involved the beginning of the left bundle.

Incidence of left bundle branch block

Katz and Pick[illegible] in a review of the electrocardiograms from 50,000 individuals, found complete left bundle branch block on 560 occasions, an incidence of approximately 1 per cent. In this same group of patients studied, the occurrence of complete right bundle branch block was 1.30%, an incidence of a little over 2 per cent.

Hiss and Lamb[illegible] have reviewed the electrocardiographic findings in 122,043 male subjects in the United States Air Force ranging from 16 to over 50 years of age. Complete left bundle branch block was encountered in 17 subjects. They noted that despite the large population of 44,731 subjects under the age of 25 years, not a single case of complete left bundle branch block was found. The incidence rate of left bundle branch block in subjects under the age of 35 was 0.5 per 10,000 subjects and 3.0 per 10,000 subjects who were 35 years of age and older. These authors commented that the apparent rarity of complete left bundle branch block in healthy subjects under the age of 25 and its rare occurrence in subjects under the age of 35 indicate that left bundle branch block in an asymptomatic population is commonly an acquired abnormality. They further observed that in view of the large population studies it is unlikely that complete left bundle branch block occurs as an isolated asymptomatic congenital abnormality.

Epidemiology of left bundle branch block

Ostrander[illegible] has recently reported an epidemiological study of bundle branch block. Electrocardiograms were recorded on 8,641 persons of all ages. Eighteen individuals, 6 men and 12 women, had left bundle branch block. The youngest in this group with left bundle branch block was 38 years old, whereas the majority were over 50 years old. In this same study Ostrander found an equal number (18 persons) with right bundle branch block. He found that those with bundle branch block did not differ significantly from the remainder of the population in levels of blood pressure, serum cholesterol, blood sugar, and body weight, although these values were far above "ideal" ranges.

All 36 persons were over 20 years of age and 67 per cent were over 60. He concluded that the age distribution suggested that bundle branch block is an acquired condition. He found very few cases in the more numberous younger age groups in the population studied. The 67 per cent of cases of bundle branch block in persons over 60 years of age occurred in only the 11 per cent of the total population over 60 years of age.

Prognosis

In 1944 White[illegible] wrote: "Bundle branch block of slight degree may be a relatively unimportant accidental discovery or it may be associated with serious and rapidly fatal heart disease such as extensive infarction from coronary thrombosis. It may exist unchanged for many years and allow full activity, or it may change in the course of weeks or months, increasing in degree along with symptoms and signs of progressive heart failure. It may be entirely unimportant in rare cases occurring as a more or less transient effect of vagal stimulation or of fatigue in excessive tachycardia. Of itself it is not fatal, but each case must be analyzed carefully. Although the prognosis is to be based largely on other evidence of heart disease, the finding of true bundle branch block of high degree renders the prognosis necessarily more guarded. The average duration of life after its discovery is in the present state of inadequate follow-up analysis about three years, ranging from a few weeks to twenty years or more.

"There seem to be two general clinical groups of cases with bundle branch block: (1) that with a rapidly bad prognosis based largely on the presence of evidence of extensive heart disease, usually considerable enlargement and some degree of myocardial or coronary insufficiency, and (2) that with a fairly good prognosis of years of life and activity in which the bundle branch block is the only abnormal finding. despite this general trend accurate

prognosis in an individual case is usually impossible.

In 1951 Johnson and associates[11] reported on the survival time in a consecutive series of 555 patients with left bundle branch block. The period of observation ranged from 1937 to 1948. The average survival period was 3.3 years. The 356 patients who survived the first year had an average survival period of 4.9 years. There were 335 males and 220 females in their series. Almost 90 per cent of the patients were over 50 years of age. The highest incidence of left bundle branch block occurred in the seventh decade and included 35 per cent of their patients. A survival period of less than 1 year was found in 170 patients (31 per cent of the total series). A total of 121 patients, or 21 per cent of the entire series, survived longer than 5 years after the diagnosis of left bundle branch block had been made. One patient was still alive 18 years after the diagnosis of left bundle branch block. Two patients were alive after 13 years and 1 patient was known to have lived for 24 years. These workers observed that survival periods were longer in the younger than in the older patients. Heart size was definitely related to survival time. Patients who had no cardiac enlargement survived 4.3 years, whereas those with greatly enlarged hearts survived only 2.5 years. Those patients with hearts of normal size had approximately 1 year longer survival than the average patient, whereas those with marked enlargement of the heart had about 1 year shorter survival period.

In this series[11] the most common etiological relationship with left bundle branch block was hypertension (342 patients). One hundred twenty two of these patients also had clinical evidence of coronary artery disease. There was a total of 209 patients who had coronary heart disease. A total of 429 patients, or 77 per cent, of the series manifested either hypertension or coronary artery disease, or both. The relationship of the underlying heart disease to the survival time showed the poorest prognosis in those with coronary artery disease; survival time was 3 years as compared to 3.3 years for the entire series. There were 357 deaths during the period of observation and 71 per cent of these were due directly to heart disease, with the majority of patients having either congestive heart failure or myocardial infarction.

In a companion article, Messer and associates[106] compared the prognosis of right and left bundle branch block and concluded that right bundle branch block showed a slightly better prognosis than left, although in patients over the age of 50 years there was only a slight difference between the average survival periods of right and left bundle branch block, either in the total number of patients or in the group who survived the first year. Patients under the age of 50 years who had right bundle branch block had a longer survival period, except those between the ages of 30 and 40 years. The explanation offered was the high proportion of females with rheumatic heart disease in this latter group who had right bundle branch block and showed the shortest survival period. These authors observed that "The electrocardiographic pattern of either right or left bundle branch block, while indicating heart disease, does not per se permit a diagnosis. A long survival time free of symptoms is not incompatible with this electrocardiographic finding. A complete evaluation of the patient's cardiac status, his functional reserve, and frequently the progression of his disease over a period of time is necessary before the prognosis can be estimated. Our figures indicate a more favorable outlook than that of earlier studies, probably because of the increasing frequency with which electrocardiograms are being taken on patients with minimal cardiac symptoms.

Rodstein and associates[107] in 1951 reported a mortality study on cases of bundle branch block. These workers collected 193 cases of bundle branch block from the files of the Equitable Life Assurance Society of the United States. The majority of these individuals had little or no physical impairment, and most were not under medical care at the time when their lesion was discovered. In the series, 131 had right bundle branch block and 52 had left bundle branch block. These workers concluded that bundle branch block is an infrequent lesion in the general population since

their collection of cases was secured from approximately 30,000 electrocardiograms reviewed. They further observed that right bundle branch block was of much greater frequency than left bundle branch block, particularly in the younger age group. More than 50 per cent of their subjects had little or no demonstrable cardiac involvement. These workers also observed that the difference between the mortality in right bundle branch block and that in left bundle branch block was relatively slight. They observed that the most significant finding in their study was the unexpected observation that bundle branch block in the absence of other cardiovascular abnormalities was not attended by a high mortality rate.[1,7,19] They also commented that, in the past, bundle branch block had been regarded as being of ominous significance, but they concluded that their study indicated that this was far from the truth.

Bauer[3] has recently reported a clinical study of 167 patients with bundle branch block. Follow-up information was available on 59 of these patients who had left bundle branch block. Twenty-five with left bundle branch block died during the period of observation, giving a mortality rate of his series of 42 per cent. Of these patients with left bundle branch block, 80 per cent died from heart failure or myocardial infarction. Eleven of the 25 deaths occurred within 1 year after recognition of left bundle branch block, 14 within 2 years, 16 within 3 years, 18 within 4 years, 22 within 5 years, and 24 within 6 years. In all the fatal cases death occurred within 7 years of diagnosis. Of the 34 survivors, 1 patient was known to have sustained a myocardial infarction complicated by left bundle branch block in 1941, giving a survival of 27 years at the time of the writing of his article. Ten patients have been followed up to 5 years, and 20 patients up to 3 years. In this series the 1-year survival rate was 77 per cent, the 3-year survival rate was 71 per cent, and the 5-year survival rate was 57 per cent.

In contrast, Bauer[11] found the survival rate in his follow-up of 96 patients with right bundle branch block to be 79 per cent. The 1-year survival rate in patients with right bundle branch block was 92 per cent, the 3-year survival rate was 82 per cent, and the 5-year survival rate was 66 per cent. He concluded that his study confirmed that the prognosis of left bundle branch block is more serious than that of right bundle branch block, but that the outlook even for left bundle branch block is much less unfavorable than has been indicated by the statistics previously quoted in the literature.[21] That the prognosis in his total series of bundle branch block was more favorable than that reported in the literature, Bauer explained as being due probably to the fact that his series was collected mainly from ambulant patients seen in private practice, whereas most of the other series were reviews of patients seen in hospitals and included cases of a more advanced nature.

Rodstein and associates[197] found a mortality ratio* of 261 per cent in their 52 cases of left bundle branch block with 11 deaths. Singer[199] has stated that in left bundle branch block the mortality ratio for the "better" cases is double the ratings for complete right bundle branch block. He stated this has been based on the evidence of a higher proportion of organic heart disease in cases of left bundle branch block. Langner[200] has stated that for complete left bundle branch block to occur both main branches have to be damaged, which indicates more extensive involvement of the endocardial tissue than is required to produce right bundle branch block. He believes that this is why left bundle branch block is more serious than right bundle branch block.

Vazifdar and Levine[201] reported 4 cases of left bundle branch block without apparent organic heart disease and referred to them as "benign." Wolfram[202] added 7 more cases of left bundle branch block without significant heart disease. DeForest[203] reported 4 cases of left bundle branch block in the same family and considered at least 3 of these to be "benign" left bundle branch block.

The author knows of at least 2 other cases of left bundle branch block in otherwise perfectly healthy middle-aged men.[14,204] Both men are in their forties and the

*Ratio of actual deaths to expected deaths on the basis of standard insurance company mortality tables.

bundle branch block was an incidental finding in the course of a routine examination. The period of observation has been 2 to 3 years, and to date, no other cardiac signs or symptoms have developed. One of these men plays tennis regularly.

In 1947 Wilson, Rosenbaum and Johnston[illegible] made the following observations (which are still appropriate today): "When a physician is confronted by a man with bundle branch block, a knowledge of what is wrong with the average man who exhibits this electrocardiographic abnormality is of no great value to the doctor and is of no interest to the patient. What is to be done depends upon the nature of the underlying disease responsible for the conduction defect. If the physician cannot diagnose this disease on the basis of unequivocal evidence, he is not justified in making a diagnosis based on the most frequent cause of bundle branch block, or a prognosis based on the average length of life after the discovery of this disorder."

Therapy

There is no specific therapy for left bundle branch block. Treatment is directed at the underlying heart disease. White[illegible] stated that complications, such as congestive heart failure and angina pectoris, should be treated without regard to the presence of the bundle branch block.

It should be re-emphasized that in the presence of left bundle branch block the electrocardiographic pattern diagnostic of myocardial infarction may often be masked. In cases, then, of left bundle branch block in which a recent myocardial infarction is suspected, reliance should not lay too heavily on the electrocardiogram but instead on the clinical picture including enzyme studies, and appropriate therapy should be instituted.

The presence of left bundle branch block should in no way interfere with the administration of digitalis when needed. Katz[illegible] has pointed out, however, that when digitalis leads to ventricular premature contractions, the danger of ventricular fibrillation is increased by the presence of intraventricular block.

Katz[illegible] has stated that quinidine is usually contraindicated in the presence of intraventricular block; however, he emphasized that contradictorily it is more important to use quinidine in allaying ectopic rhythms when block is present than when it is absent. Bellet[11] also observed that quinidine should be given with caution in patients who have bundle branch block, since toxic effects may occur with a relatively small dose. He further stated, however, that bundle branch block should not prevent the use of quinidine in selected cases.

The author would concur in the cautious use of quinidine, even in the presence of left bundle branch block, when it is indicated in controlling or preventing arrhythmias.

Note: Diagram 2 of Fig. 14 in Part I of this article more closely follows the findings of Bourassa, Boiteau and Allenstein[illegible] than those of Braunwald and Morrow.[illegible] The latter authors found that the average time interval between the onset of the QRS complex and the onset of ventricular contraction was identical for both ventricles, 0.068 second. See text.

Cardiac pacing

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A multitude of cardiac pacemakers, both internal and external, of varying designs and manufacture, are now available. Although acute and chronic electrical stimulation of the heart is of demonstrated efficacy for maintenance of patients with complete heart block, division of opinion still exists as to the preferred approach to therapy. Long-term transvenous endocardial pacing and direct myocardial stimulation with pacemakers both synchronous and asynchronous to the atrium are all available and have various clinical advantages.

External stimulation

1. The original pacemaker, variations of which continue in clinical use, is the external pacemaker providing a 2-msec. shock of 50 to 150 volts across the closed chest. This valuable approach is most rapidly applied, requires little skill in application, and is basic for the emergency situation. Its use is painful to the patient, and sedation is usually required. Patients maintained for substantial periods on such stimulation may develop cutaneous burns at the site of electrode placement.

2. For both short-term and long-term pacing for early control of patients with complete heart block, and for prolonged control in some, an electrode catheter (passed through the external jugular vein) may be utilized. In skilled hands control is rapidly achieved with a high degree of safety. It avoids a thoracotomy, is comfortable, and when carefully supervised permits indefinite maintenance of some patients on an ambulatory outpatient basis. Neither short-term nor long-term resistance to stimulation has occurred. Although transvenous pacing can be utilized for any age group, it is especially worth while when thoracotomy is contraindicated. The catheter may be passed from any peripheral vein, although stability of position and consistency of pacing requires that a site be selected from which there is little motion relative to the thorax. Thus, passage from either the external jugular or femoral vein is desirable, whereas passage from the basilic vein is undesirable. The occurrence of malposition is usually related to a poor choice of vein or improper initial ventricular placement.

The presence of a foreign body (cardiac catheter) entering the external jugular vein at the root of the neck from an extracutaneous position may be a source of local cutaneous and blood stream infection during a long-term maintenance when the power pack is worn externally. When systemic infection occurs, it must be dealt with promptly by removal of the infected catheter and institution of vigorous antibiotic therapy. Several groups have described satisfactory long-term maintenance with a totally buried pacemaker-catheter assembly. Such an assembly eliminates the prob-

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lems of infection and of an external appliance. With this device long term stability of position, unchanged sensitivity to stimulation and effective ambulatory outpatient pacing have been accomplished A number of authorities consider such implanted catheter pacemakers to be the treatment of choice at the present time. Although perforation of the right ventricle with a pacer catheter is possible when the external jugular approach is utilized such an event is rare.

3 Direct stimulation of the left ventricular myocardium by a special electrode wire passed percutaneously through a needle in the chest provides a rapid approach to effective cardiac control However the percutaneously inserted electrode transverses the skin and infection and dislodgment are possible. Only short term use can be undertaken

Direct myocardial stimulation Three major component groups form an implantable pacemaker These are (1) the power source (2) the electronic circuit, and (3) the leads and electrodes.

1 Mercury cells are employed to provide electrical energy and despite their estimated energy capacity of 5 years, no pacemaker manufacturer's warranty extends beyond 3 years. When the mercury cells are exhausted replacement of the pacemaker pulse generator must be performed surgically

2. The electronic circuit has been troublesome. Faulty components and internal short circuits have caused premature cessation of stimulation. An additional hazard has been "runaway pacemaker" in which the rate may rise to several hundred impulses per minute, with consequent induction of ventricular fibrillation. Although infrequent, this variety of failure has been responsible for two out of seven deaths in the late postoperative period in the author's series. In order to minimize this possibility early replacement of the pacemaker pulse generator has been suggested by at least one manufacturer

One of the major causes of circuit failure has been the unavailability at this time of adequate material to insure the protection of the circuit itself from the incursion of body fluids. Both the silicone rubber coating and the epoxy resin used to encase the cells and circuit reach a more or less rapid equilibrium with the body fluid medium and allow destruction of the circuit

3 The least reliable component is the system of wire leads from the pulse generator to the heart. Braided stainless steel leads, coiled springs of platinum-iridium and coiled springs of Elgiloy are all in use Approximately 10 per cent of wire leads of all designs have broken down in the short period of 5 years of internal pacemaker use. Wire leads of the most modern design still are complicated by premature breakage, although such breakage is now not usually apparent during the first year of use The use of newer materials, such as Elgiloy which has greater resistance to flexion fatigue, may provide greater durability for the lead system Coiled wire springs of Elgiloy however are usable only as the electrolytically inactive negative terminal of a bipolar system. The use of noble metal plating over stainless steel will probably not resolve this breakage problem, since the presence of dissimilar metals within an electrolytic system produces an enhanced electrolytic effect.

Two types of direct myocardial stimulating implant pacemakers are available (1) fixed-rate and (2) synchronous. Four United States manufacturers (Medtronic, Electrodyne, Cordis, and General Electric) have fixed-rate pacemakers available. All use mercury cells of identical manufacture (T R. Mallory) as the energy source Three utilize a pulse of approximately 2 msec. in duration and the fourth uses a pulse of 2.5 to 3 0 msec in duration The factory set rate is between 60 and 70 beats per minute. The most widely used of the units (Medtronic) provides a pre-set output of 3 Ma. and utilizes coiled-spring electrodes of platinum-iridium. There is increasing although as yet inconclusive, evidence that 3 Ma does not provide sufficient output for consistent stimulation for all patients in the face of a normal increase in threshold and myocardial resistance. The other three units have fixed outputs of 5 10 and 14 Ma. respectively Two of these units use coated braided stainless steel electrodes (Electrodyne and General Electric) and the third (Cordis) uses coiled platinum iridium or Elgiloy leads.

The cardiac output with these fixed-rate

units has been satisfactory and has been demonstrated to vary widely in response to changes in activity and body requirements.

The P wave synchronous pacemaker (Cordis Atricor) which utilizes an atrial lead as a pickup stimulates the ventricle as a response to the atrial P wave. Maximum and minimum rates are pre-set so that breakage of the atrial lead or atrial arrhythmia permits a return to a basic atrial rate of 60. A maximum ventricular rate of 120 is set, so that electronically and atrially induced ventricular tachycardia cannot occur. This unit is the most physiologic of the units available and is especially desirable for young people in whom the addition of the atrial component to cardiac output and the ability to increase cardiac rate with activity are undeniably significant features. The P wave response may not be suitable for certain older persons, some of whom have been reported to lower cardiac output at rates of 80 to 90 per minute and even develop angina. The unit is heavier than the average and its group of three leads (two ventricular and one atrial) end in a plug that connects to the pacemaker. This plug arrangement is especially liable to produce flexion stress on the leads, so that premature wire fatigue and fracture have been demonstrated to occur. Elgiloy leads which will reduce this complication are now available, at the user's option.

At their best pacemaker units provide a return to a state of almost complete cardiac normality. For persons whose cardiac disease is primarily that of atrioventricular dissociation with Stokes-Adams syndrome a return to almost full activity is possible. At their worst implanted pacemakers may fail because of rising resistance to electrical stimulation, component failure, and lead breaks, thus requiring repeated operative procedures.

For long term maintenance the implant technique utilizing any of the available pacer units, or the jugular transvenous approach, external or internal, may be utilized. There has been gradual acceptance of the implanted transvenous pacemaker technique and its utilization represents at this time a growing proportion of the total number of pacemakers implanted both in the United States and abroad. Implantation of a transvenous pacemaker avoids thoracotomy and general anesthesia. Although malfunction of the pulse generator may be identical to that which occurs with direct myocardial stimulation, repair and replacement can be made as a nonoperating room procedure under local anesthesia, usually in a cardiac catheterization laboratory. Although the potential for breakage still exists, the catheter itself is stressed far less mechanically and because the electrodes themselves are subjected to little mechanical stress they may be constructed of totally inert metal such as pure platinum.

Present recommendation. At this time all patients who require an artificial pacemaker should be started on transvenous pacing as the initial mode of electrical management, utilizing either the rapid femoral route for the short term period or the external jugular route for longer periods. This approach allows control of Stokes-Adams seizures, congestive heart failure, and the cerebral and renal manifestations of low cardiac output caused by slow cardiac rate and episodes of circulatory arrest.

For the patient admitted with recurrent Stokes-Adams seizures, for whom immediate electronic stimulation is mandatory, external stimulation followed by passage of the catheter via the femoral vein is indicated. Even when drug therapy can control the situation briefly, the femoral vein approach is now preferred, so that the external jugular vein will be available for definitive transvenous implantation of the pacemaker.

Although implantation via thoracotomy may be utilized, especially when a synchronous pacer is indicated, it was in this very group, because of relatively normal activity, that lead breaks occurred more frequently.

The malfunction rate of implanted pacemakers has been sufficiently high (with each repair requiring subcutaneous or intrathoracic exploration, or both) so that we consider transvenous pacing to be the procedure of choice at the present time.

Future pacemakers may utilize miniaturized radio-frequency rechargeable pulse generators to stimulate the heart via conventional leads or catheters or may be implanted directly upon the myocardium. Electrical energy may be derived from piezoelectric crystals driven by body mo-

tion or from fuel cells using body fluids as the electrolyte. These developments offer the prospect of greater resistance to wear and indefinite functioning without need for reoperation. These exciting developments, however, are not yet clinically available.

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Annotations

The effects of surgery under general anesthesia on the ischemic electrocardiogram

The assessment of the risks of surgery under general anesthesia to patients with ischemic heart disease is becoming more important with the increasing incidence of the disease and the increasing scope of modern surgery. A knowledge of these risks in terms of mortality and morbidity is needed so that they can be weighed against the potential benefits of operative procedure and so that precautionary measures can be taken.

A wide variation in operative mortality has been reported in different series of patients with ischemic heart disease but Nachlas and associates reviewed the published data and concluded that the over-all mortality was two to three times higher than would be expected in unselected patients. Their own figures showed that postoperative complications were also over twice as frequent in patients with arteriosclerotic heart disease as in a control group. A high incidence of electrocardiographic deterioration has been noted by Driscoll and associates who recorded electrocardiograms (ECGs) before and after operation in 496 unselected patients marked fresh ischemic changes occurred postoperatively in 23 per cent of 145 patients in the series with chronic coronary heart disease, hypertension, diabetes or abnormal preoperative ECGs, *whereas similar changes* occurred in less than 3 per cent of the other 351 patients without these conditions.

A selected series of patients with known ischemic heart disease or hypertension has recently been studied in a similar manner. The series comprised consecutive patients undergoing operation in whom the preoperative ECGs were known to show definite evidence of ischemic heart disease or who had hypertension, defined as a systolic pressure of 200 mm. Hg and over or a diastolic pressure of 120 mm. Hg and over. Excluded from the study were patients with left bundle branch block because of the difficulty in detecting fresh ischemia from their tracings and patients in whom thoracic surgery or dressings precluded the use of conventional precordial leads. Arrangements were made before surgery for a tracing to be taken the day after operation when this was markedly changed from the preoperative ECG another tracing was usually taken 3 days later. A total of 217 sets of tracings were analyzed; all but 12 of the preoperative tracings were judged to show ischemia or had S-T and T changes of left ventricular strain. The preoperative and postoperative tracings were reported in pairs without prior knowledge of the order in which they had been taken and any changes were noted. Forty-eight patients (22 per cent) developed significant electrocardiographic deterioration postoperatively and of these 3 had changes which indicated probable fresh infarction. Two other patients included in the series, who showed no early postoperative ECG deterioration, developed severe chest pain within a week of operation and then had unequivocal evidence of transmural anterior infarction. Therefore, the over all incidence of known or suspected infarction under anesthesia or in the early postoperative period was 5 (2.3 per cent) out of 217.

Minor changes were noted in 71 ECGs of these, 48 showed slight worsening and 23 showed slight improvement postoperatively. If surgery and anesthesia did not influence these minor variations, one would have expected similar numbers to improve and deteriorate. Although these changes were not pathognomonic of fresh myocardial ischemia, great care was taken to exclude differences due to variations in the electrical position of the heart and the position of the electrodes, and also changes due to the effects of tachycardia.

No fresh postoperative arrhythmias were noted *in any of the patients in the series.*

An attempt was made to identify any factors which were particularly associated with electrocardiographic deterioration. Sex, age and the preoperative levels of blood pressure appeared to have little influence on the results obtained. The methods of anesthesia employed were varied, but there was no detectable increased risk associated with any type of premedication technique, or anesthetic agent. There was, however, an increased incidence of ECG deterioration in patients undergoing abdominal surgery especially that involving incision of the peritoneum in patients having operations lasting more than 2 hours, and in those known to have had pronounced falls in blood pressure under anesthesia. The dangers of lengthy operations and of hypotension during operation to patients with ischemic heart disease have been noted in other studies.[1-4]

Follow-up tracings were taken 4 days after operation in 32 of the 48 patients who had marked electrocardiographic deterioration postoperatively. The fresh ischemic changes had resolved in only 13 of the 32 with improvement in some of the others. Thus in most cases the changes were more than fleeting

alterations in pattern, and represented muscle injury or muscle death. This was in patients who already had heart disease with some limitation of cardiac reserve, and who were least able to afford further myocardial damage. The damage suffered by these patients gave rise to no symptoms or signs and would not have been detected but for the study which was being made at the time. Even the 3 cases of probable myocardial infarction were asymptomatic, doubtless because they occurred under anesthesia and under the influence of postoperative analgesic drugs. The occurrence of myocardial infarction during or after operation was stressed by Mendelsohn and Monheit, who suggested that the incidence of this condition was considerably higher than was generally suspected. Driscoll and associates arrived at a similar conclusion.

It is not difficult to enumerate the factors associated with surgery under general anesthesia which may be particularly hazardous to the patient with ischemic heart disease. Anesthesia can be responsible for anoxia due to laryngeal spasm, hypoventilation, and ventilation-perfusion inequality, and also for falls in cardiac output due to positive pressure respiration, myocardial depression, and cardiac arrhythmias. Surgery carries its own dangers from shock, and perhaps from reflex falls in cardiac output and coronary vasoconstriction evoked by manipulation of the peritoneum and viscera. In the postoperative phase pain and analgesic drugs may cause hypoventilation and ventilation-perfusion inequality can persist as an additional cause of lowered arterial oxygen saturation. Further research may well be directed to defining more precisely the relative importance of these factors so that suitable measures may be taken to avoid those which most frequently increase myocardial ischemia. Greater emphasis needs to be placed on the identification of patients who are at risk: preoperative ECGs should be taken on all elderly patients, as well as on those with symptoms and signs suggestive of arterial disease.

There would be no complacency about the risk faced by patients with ischemic heart disease undergoing surgery if the cardiac damage they had suffered were readily apparent. The fact that it can so frequently remain undetected places a special responsibility on the anesthetist and surgeon and calls for a high degree of technical skill and clinical judgment.

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The management of childhood nephrosis

With the advent of prolonged corticosteroid therapy, the last decade has witnessed a major breakthrough in the management of the nephrotic child and a marked improvement in his immediate prognosis. The same degree of optimism has not been justified with respect to the long-term outcome, particularly the ultimate mortality from renal failure.[1,2] A recent review of our experience with children suffering from "nephrosis" during the three therapeutic eras—preantibiotic, antibiotic, and steroid—makes us believe, however, that late prognosis can also be significantly improved with adequate steroid treatment.

The term "nephrosis" in the present context is used to connote the usually idiopathic childhood syndrome of massive proteinuria, hypoproteinemia, hyperlipemia, and edema, without, at least in the early stages of the disease, persistent hematuria, hypertension, or renal failure. Typical "foot process" and basement-membrane changes seen by electron-

microscopy characterize the condition histologically.

Spontaneous recovery of 40 to 50 per cent of the patients within 2 to 3 years of onset has been the rule provided that the child does not succumb to infection.[1, 2] This tendency of the disease was brought into sharp focus by the advent of effective antibacterial agents which so curtailed mortality due to pneumococcal peritonitis. As used initially for short treatment periods, steroids and ACTH did little to change the course of the disease: their particularly favorable influence was noted when prolonged maintenance therapy was introduced. Although relapses are still common today and a certain proportion of the patients develops progressive renal failure and dies, the clinical course of the disease has been altered beyond recognition. Modern treatment has decreased morbidity to such an extent that the average child can look forward to leading a reasonably normal life, except during periods of acute exacerbation. Mortality from infections has been almost eliminated and that from renal failure, diminished. Life has been prolonged even in the group of children with renal failure who finally die of uremia and hypertension.

Supportive therapy is of the utmost importance in the management of nephrosis. The details have been discussed in several recent articles.[2-4] These include the control of edema with the use of infusions of albumin, diuretics, and, rarely, paracentesis; maintenance of adequate nutrition; prevention and control of infection; and management of hypertension and renal failure. The greatest ingenuity may be required to deal effectively with the emotional impact of this chronic disease on the young child.

The different preparations of steroids and various schedules of dosage have failed to show a significant superiority of one over the others. As soon as the diagnosis has been established, we begin treatment with cortisone, 300 mg. per square meter per day, or prednisone in an equivalent dose. The amount of drug is reduced to 200 mg. per square meter per day after 6 weeks of therapy or when remission has occurred, whichever is earlier. (A remission is taken to mean disappearance of edema and proteinuria, elevation of serum protein to 6 Gm. per cent or over, and reduction of serum cholesterol to 200 mg. per cent or less.) Steroids are continued at this dose level for 3 months of uninterrupted remission. Relapses are treated promptly in a fashion similar to that used for the initial episode. Most patients require therapy for 1½ to 2 years before achieving prolonged remission. Even then, the risk of late relapses persist.

Side effects of steroid therapy are frequent and occasionally serious. In an attempt to reduce these, we have recently treated with steroids on an alternate-day schedule 20 patients representing a wide spectrum of the problems of childhood nephrosis. The total amount of drug for 2 days has been given in a single morning dose every 48 hours,[16] as suggested by Harter and associates.[17] The effectiveness of this schedule over the still relatively short period of follow up extending from 3 to 20 months has been similar to that of the usual 8-hourly dosage regimen. Except for mild rounding of the face there has been a remarkable freedom from Cushingoid changes, electrolyte or growth disturbances, hypertension, convulsions, and other side effects associated with steroid therapy of conventional schedule. Fasting plasma cortisol levels in 3 patients have failed to show any evidence of adrenocortical suppression.

A small percentage of nephrotic patients fails to respond to steroid therapy. Several studies have pointed out correlation of such refractoriness with functional[18] or histologic[12, 18] severity of the glomerular lesion, age of the patient,[14,16,17] the duration of disease before treatment is begun[18] and more recently immunopathologic findings in the kidneys.[19] These patients present a formidable therapeutic problem. Antimetabolite or immunosuppressive drugs, including nitrogen mustard, 6-thioguanine, 6-mercaptopurine, cyclophosphamide and azathioprine, have proved to be of some value in their management.[20, 21] We obtained complete or partial remission after 10 of 13 courses of treatment with nitrogen mustard or cyclophosphamide. In another steroid-resistant patient, azathioprine (Imuran) was used twice with success. Meanwhile, steroids were continued in the usual dose. On the basis of this experience we believe that immunosuppressive drugs have a definite place in the treatment of nephrosis.

Although early and prolonged steroid therapy with judicious use of various supportive measures leads to recovery in the majority of patients, the management of nephrosis is by no means easy. The unpredictable, long and fluctuating course of the disease challenges the equanimity and patience of the physician and the parents alike. Efforts directed at further sophistication of steroid therapy, exploration of the role of antimetabolites in resistant cases, and that of gammaglobulin in prevention of relapses due to infection hold promise of even greater therapeutic dividends.

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On the mechanism of exaggerated natriuresis in hypertensive man

The mechanism of the augmented natriuretic response to sodium loading which occurs in hypertensive subjects is unknown. The recent suggestion in these pages that this exaggerated natriuresis may result from a chronically enhanced concentration of medullary sodium is of interest because it stimulates new thinking about the phenomenon and invites consideration of indirect data, presently available, which appear to argue against this suggestion.

If the medulla of hypertensive man has indeed an abnormally high concentration of sodium, then an enhanced capacity to concentrate the urine might be expected in such subjects. In fact, however, essential hypertension does not appear to augment concentrating capacity in man.

During water diuresis, sodium is washed out of the renal medulla. The fact that a hypertensive subject may exhibit exaggerated natriuresis during maximal water diuresis[4] therefore indicates that exaggerated natriuresis can still occur even when the concentration of medullary sodium is decreased. The fact that clearance of free water increased normally in this study with increasing delivery of sodium to the diluting segment further shows that limited tubular capacity to reabsorb sodium could not be demonstrated.

In fact, it appears that exaggerated natriuresis is not the result of a limited tubular capacity for reabsorption of sodium since it may occur with decreasing glomerular filtration rate[4] or decreasing concentration of serum sodium, and even without the infusion of saline. Thus, an overflow natriuresis

resulting from the presentation of an increased load of sodium to tubules of limited reabsorptive capacity cannot be involved. The problem instead seems to be why the tubules of the hypertensive patient which are capable of rejecting appropriately small amounts of sodium in response to certain stimuli nevertheless reject abnormally large amounts of sodium in response to a variety of other stimuli including water loading, ingestion of beer, and emotional stimuli, as well as the infusion of sodium. This flexible tubular mechanism for the rejection of sodium continues to challenge our understanding.

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Arcus senilis and coronary artery disease

Early observers variously attributed arcus senilis to dryness of the cornea, local vascular impairment, chronic inflammation, or even pressure from the eyelids. Lawrence[1] and Middlemore[2] were among the first to compare an arcus with the intimal lesion in the arteries of the aging subject, whereas Canton, after histologic examination, declared it to be a fatty degeneration and considered that its presence was likely to be associated with fatty degeneration of the heart. Parsons demonstrated a cholesterol-like substance in affected corneas, and this view of arcus as a lipoid infiltration was confirmed by Lowenstein and others who produced an arcus in animals by feeding a cholesterol-rich diet. Detailed histologic observations were made by Cogan and Kuwabara. They showed that the lipid of the arcus, present in the membranes and stroma of the cornea, comprises cholesterol, phospholipid, and neutral fat, and the large amounts which may be present together with the absence of any underlying degenerative change led them to reject the idea that arcus was a simple senile degeneration and to postulate that the fat is derived from the blood and becomes secondarily bound to the corneal tissue.

There have been many studies of the plasma lipids in relation to arcus formation. Forsius[10] found that the mean serum cholesterol was higher in the patients with an arcus in each age-group from the second to the seventh decade; he also found differences in cholesterol esters, total lipids, alpha-lipoproteins, and the cholesterol/phospholipid ratio. In Lindholm's study[11] there was no correlation of serum cholesterol with the degree of arcus, but Pomerantz[12] found that most patients with a significant arcus had an elevated level of serum cholesterol. Finley and associates[13] demonstrated an association of arcus senilis with diminished fat tolerance and high plasma triglyceride levels in young men, but they found no close association with hypercholesterolemia. Shanoff and Little[14] concluded that up to the age of 60 the presence of an arcus was positively correlated with serum cholesterol and phospholipid but not with serum lipoprotein levels. Rifkind[15] showed that serum cholesterol and beta-lipoprotein levels were significantly higher in healthy men with an arcus than in those without.

Several studies[8,16] have demonstrated the rising incidence of arcus senilis with advancing age and its greater frequency in men than in women. Many attempts have been made to associate an arcus senilis with vascular disease, and Virchow[17] considered that the presence of an arcus was a definite aid in the diagnosis of heart disease. Some

subsequent authors[illegible] have considered that arcus is associated with arteriosclerosis, whereas others[illegible] found no evidence of an association.

Lindholm,[11] in his comprehensive study, found no correlation of arcus with arteriosclerosis, except in men who were 40 to 49 years of age. Beaumont and associates[illegible] found a significant increase in the incidence of arcus senilis among men with angina pectoris or cardiac infarction; this was most marked in those in the 30-39-year age group and became progressively less in those in the next two decades. Pomerantz[12] found a significant association of arcus with cardiac infarction in men up to the age of 58 only. Rodstein and Zeman[illegible] found no general correlation of arcus with arteriosclerosis, but they noted an excess of electrocardiographic abnormalities in elderly subjects with marked arcus senilis. An increased incidence of arcus in postcardiac-infarction patients was found by Shanoff and Little[14] in those under the age of 40, and by Rifkind[15] in those in the 40-49-year age group.

In view of the still prevalent clinical impression that the presence of an arcus is a useful sign of arterial disease, a limited study of both healthy and atherosclerotic subjects was undertaken. The incidence of arcus in men and women of different ages was compared in 250 healthy subjects. The incidence rose progressively with age, no arcus being observed in the 20-29-year age group, whereas 59 per cent of men and 41 per cent of women in the 60-69-year age group showed an arcus. At all ages the incidence was higher in men than in women, although the sex difference diminished with advancing age.[17] When 100 male postcardiac-infarction patients who were between 40 and 69 years of age were compared with 100 age-matched male controls, no significant difference in the incidence of arcus was found either in the whole groups or in the three decades treated separately. In both groups a similar rise in incidence with advancing age was noted.[illegible]

Both obesity[illegible] and hypertension[illegible] have been shown to be associated with an increased incidence of coronary artery disease. In the group of postcardiac-infarction subjects no significant difference in height, weight, ponderal index, systolic blood pressure, or diastolic blood pressure was demonstrated between those who had an arcus senilis and those who had no arcus.

Many patients with ischemic heart disease have higher levels of serum cholesterol and mucoproteins and plasma fibrinogen than normal subjects.[illegible] In the middle-aged postcardiac-infarction subjects, neither serum cholesterol nor mucoprotein levels differed significantly according to the presence or absence of an arcus senilis. However, all of the subjects who had a serum cholesterol level greater than 350 mg. per 100 ml. were noted to have an arcus. Levels of plasma fibrinogen were significantly higher in postcardiac-infarction subjects with an arcus than in those without.[17]

In summary, arcus senilis increases in frequency with advancing age, and it appears earlier in men than in women. It is a frequent accompaniment of pronounced hypercholesterolemia. We consider that its presence or absence in the middle-aged or elderly is of little clinical significance; however, its appearance in men under the age of 40 suggests an alteration in plasma lipids and an increased susceptibility to coronary artery disease.

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Letter to the Editor

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Antipolarization

To the Editor

According to Dorland's *Medical Dictionary*, depolarization is the process or act of neutralizing polarity, and to depolarize means to reduce to a nonpolarized condition, to deprive of polarity.

These are in keeping with the meaning of *de*, a Latin prefix, which often signifies down or from, frequently is intensive, and sometimes negative or privative.

Apart these etymologic data it is not infrequently stated that during depolarization, the negative charge leaves the (myocardial) cell and "discharges" the positive charge of its external surface.[2,3]

This last more or less schematic presentation has been successfully used for didactic purposes and basically expresses the hypothesis of Bernstein, who supposed a breakdown of the membrane during depolarization. However, it is now almost generally accepted that the process of activation at the cell surface of the squid giant axon[4-8] and the muscle fibers of the frog heart is not one of discharge of doublets, but of reversal of electrical charges due to a migration of negative charges to the external surface and of positive charges to the internal surface. More precisely stated, the process of depolarization consists of a rapid disappearance of the resting potential, followed by reversal of polarity with the interior of the cell positive to the outside. Furthermore, according to the current ionic basis of the resting and action potentials, the resting membrane is an effective barrier to sodium but is relatively permeable to the potassium and chloride ions. In order to account for the reversal of membrane potential during activity, it is supposed that the membrane does not break down but reverses the resting condition by becoming highly and selectively permeable to sodium. Since sodium is more concentrated outside the fiber than inside, it enters the fiber and reverses the difference in potential.[10]

In this respect it is of interest that as early as 1873, Engelmann and associates[11] reported that the electrical force reverses its sign during excitation and some 15 years ago, Lepeschkin[12] stated in his book: "Whether the resting polarization of the muscle membrane is diminished, disappears completely or is actually reversed when the muscle becomes active does not matter as far as the character of the field produced is concerned. The term depolarization, as used in this book, can therefore be interpreted to mean either complete loss, diminution or reversal of polarization."

Also, many observers refer to the wave of depolarization as the wave of "accession" or "excitation," and the wave of repolarization as the wave of "regression" or "recovery," all of which terms are noncommittal as to the exact nature of the underlying electrical phenomena.

From the foregoing discussion it is evident that the term depolarization no longer corresponds to the whole process for which it had been initially introduced, and might be complemented at least for the second part of it, namely, that of reversal of polarization, the so-called overshooting. The term that we are now proposing is "antipolarization."

Actually, the prefix *anti*, from the Greek preposition *αντι*, signifies against and/or opposite. It is used in such terms as antibiotic, antibody, antidote, but also in terms such as anticlockwise, antithenar, antitragus, antarctic, etc.

The term antipolarization emphasizes the idea of polarization reversal, does not interfere with any of the terms accession or excitation, and eliminates misleading expressions, such as "neutralizing polarity," "reducing to a nonpolarized condition process," etc.

Thus, the term "depolarization" should be confined to the first stage of changing of the polarized state, which is followed by the stage of "antipolarization."

In other words, after a mechanical, chemical, or electrical stimulus, the continuous diffusion of ions which exists across the cell membrane during rest is altered, leading to a quickly diminishing density of polarization of the cell membrane (phase of decreasing polarization) until a stage is reached when no more difference in ionic concentration between the interior of the cell and the external environment is present.

At this time the phase of depolarization is completed, i.e., a "depolarized (electrically neutral) state" exists. Beyond this, antipolarization takes place, that is, polarization reappears but is of the opposite sign until a point of maximum antipolarization is reached.

This phase, which is included in the so-called depolarization, not infrequently, and indeed most appropriately, is designated as polarization reversal.[13]

It is now clear that during electrical activity of the cell, a stage of complete depolarization ("depolarized state") appears twice, once during excitation and again during recovery.

As is known, the transmembrane action potential, recorded after insertion of a microelectrode into a cell and excitation of the cell, shows an initial rapid

*This study was supported by Research Grant No. AG-65-23 from the Vermont Heart Association.

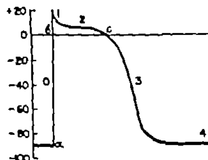


Fig. 1. Schematic record of cardiac transmembrane action potential recorded from the ventricle. Ordinate scale in millivolts. *a-b* Depolarization. *b-1*, Antipolarization. *b* and *c* Moments of depolarized or electrically neutral state. See text for discussion. (Modified from B. F. Hoffman and P. F. Cranefield, *Electrophysiology of the Heart*. New York, 1960, McGraw Hill Book Company, Inc., by permission.)

depolarization or upstroke (Phase 0) a phase of early rapid repolarization (Phase 1) a prolonged phase of slower repolarization (plateau Phase 2) a terminal phase of rapid repolarization (Phase 3) and the electrical diastole (Phase 4) (Fig. 1).

Should the proposed terminology be accepted, Phase 0 would be divided into the depolarization, i.e. the first part of it (Fig. 1 *a-b*) representing the phase of decreasing polarization and the antipolarization, i.e., the second part of it (Fig. 1 *b-1*) representing the phase of increasing polarization reversal. The spike which separates Phase 0 from Phase 1 indicates maximal antipolarization, i.e., the point of maximum polarization reversal. Whether this is actually a moment in time or has some duration, it is difficult to say with the recording speeds of today. However, it seems to be reasonable to decide that two moments of complete depolarization exist (depolarized or electrically neutral state) which coincide with the two points *b* and *c* of Fig. 1 where the transmembrane potential curve crosses the zero potential line.

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CINERADIOGRAPHY OF CARDIAC VALVES IN MAN By Jean Louis Chaillet, Utrecht 1965 Drukkerij J & D Van Der Horst, 220 pages.

The author describes his experience with cineradiography of the cardiac valves and the use of an image intensifier for direct observation of the movements of the valves. The method and apparatus used are described in detail. He summarizes the pertinent literature on the structure and movements of the cardiac valves in their respective planes. The literature on heart sounds is also summarized. Dr Chaillet describes his experience with his own method. He supports the text with photographs from cineradiographs and with many diagrams and pressure tracings. The studies are good and the presentation is clear. Unfortunately the review of the literature is not critical, but rather presents only a summary of opinions expressed by various workers. The author could improve the book by being more critical of the literature. The need for a critical evaluation is well exemplified by the discussions on the third heart sound presented on pages 63 and 64. Nevertheless, this is a good thesis which should interest cardiologists.

ELECTROCARDIOGRAMS. A SYSTEMATIC METHOD OF READING THEM By M L Armstrong, M B B.S. Bristol, 1965, John Wright & Sons, Ltd and Baltimore, 1965 Williams & Wilkins Company 64 pages Price $4 75

This book of 64 pages describes Dr Armstrong method of reading electrocardiograms. There is really nothing novel about his approach to the interpretation of tracings, but others may wish to know of his approach in order to learn whether they are satisfied with their own. Those who use computers in the interpretation of electrocardiograms may also find the book to be useful.

COMPARATIVE ATHEROSCLEROSIS. Edited by James C. Roberts, J M D F C.A.P University of California at Los Angeles and Reuben Straus, M.D., F C.A.P St. Joseph Hospital, Burbank Calif New York, 1965 Hoeber Medical Division of Harper & Row Publishers, 426 pages. Price $20.

This monograph by 56 contributors is a good one. It summarizes a conference on comparative atherosclerosis held in January 1964 The authors have gathered together many aspects of the subject for readers who may be interested in it. They discuss atherosclerosis in swine, ... es, rodents and wild animals, dogs, primates, rabbits and men. The contributors represent people who have done work in various aspects of the field. Many excellent color plates are presented the bibliography is fairly extensive (that for man is relatively meager) and the index is good. Unfortunately but for obvious reasons, the color plates are grouped as an appendix and are not displayed in the text in the immediate vicinity of the discussion. This is a good book.

CLINICAL ANTICOAGULANT THERAPY By I Myron Vigran, M D., Philadelphia, 1965 Lea & Febiger 315 pages. Price $15

This book describes in detail methods for the use of anticoagulants in the practice of medicine. Dr Vigran and his collaborators discuss blood coagulation concepts in intravascular thrombosis and vascular disease predisposing to thrombosis embolism the anticoagulants, indications and contraindications for their use, laboratory control of therapy and results in therapy including unfavorable reactions. The book contains nothing new in the field. It summarizes, in a manner the author's ideas about the problem. Dr Vigran has presented favorable points of view. For example he includes the photograph and a brief biography of only those people who have advocated anticoagulant therapy. No one is included who has had reservations as to its use. Furthermore to include contemporary physicians means that many who were not included probably wonder about the accepted significance of their work. Only 5 pages are devoted to contraindications to the use of anticoagulants. No mention is made of the fact that some physicians consider the lack of an indication with hemorrhage, cost, inconvenience and pain as serious considerations, reasons for not using anticoagulants. The author fails to indicate that, although anticoagulants are used almost routinely the incidence of myocardial infarction and death from ischemic heart disease is still not declining, but rather most likely increasing. This is surely not true for pneumococcic pneumonia since the introduction of penicillin. This is not a critical presentation of a much-discussed subject and will, therefore, not settle the differences of opinion that exist. However it will help the reader learn the opinion of those who use anticoagulants which is what the book does very well. The beginner is advised to read it critically not only the discussions of anticoagulants and their use but also the discussion of the etiology of arteriosclerosis, thrombus formation, and other related subjects. This is a small book about a big subject.

FROM AUSCULTATION TO PHONOCARDIOGRAPHY By Aldo A. Luisada, M D., Mount Sinai Hospital of Chicago. St. Louis 1965 The C. V. Mosby Company 351 pages Price $17 75

In this book, Luisada summarizes his work and that of his collaborators on auscultation and phonocardiography The subjects discussed in four sections and 35 chapters are the physiology of heart sounds and murmurs auscultation, technical aspects of phonocardiography and clinical phonocardiograph There are many original recording and diagrams to illustrate the ideas discussed in the text. Unfortunately because of the brevity of the book, Luisada fails to make clear his idea on the mechanisms of normal and abnormal sounds and leaves too much to the imagination of the reader For example, on page 166, he fails to make clear why the heart sounds are muffled in m ocarditis. Again in Figure 42 on page 94 showing the action of amyl nitrite, he fails to consider the action of the drug on the veins and pulmonary vasculature. On page 252, he states that The murmur of pulmonary insufficiency is similar to that of aortic insufficiency except that it starts barely before, or soon after the pulmonary component of the second sound instead of having the same relationship with the aortic component This is a not clear statement concerning the aortic component.

Nevertheless, this is a good book. It should be used as a supplement to others, especially those concerned with more detailed hemodynamic discussions The book presents the points of view of Luisada and his associates.

HOCHDRUCK FORSCHUNG B Prof Dr.h.c L. Heilmeyer and Priv Doz. Dr H J Holtmeier Stuttgart, 1965 Georg Thieme Verlag 402 pages, 62 tables.

This volume—Proceedings of the Second Symposium Advances in the Field of Research on Arterial Hypertension Freiburg, Br., July 18-19 1964—present in 37 articles by leading German authors a comprehensive cross section of recent progress The emphasis in this volume seems to be on drug treatment particularly α-methyldopa Of seven papers in Part I (Pharmacology Biochemistry) six are concerned with the pharmacology of this drug which appears also in the title of three articles in Part IV (Clinic and Therapy of Arterial Hypertension) and in the text of several other articles. With the emphasis on drug treatment, it is logical that the article by Holtmeier and Heilmeyer on the side effects of new antihypertensive drugs (pp. 285-354) is the largest in the volume. This material is based on an evaluation of 7,834 cases in the world literature with 170 references, and its organization in tabular form is excellent. The fewest side effects are observed with α-methyldopa and diuretics in combination with restriction of NaCl

Since it is, of course, not possible to discuss in detail the numerous articles of this volume, we shall limit our remarks to a few arbitrarily selected communications as examples of the diversified content. In Part II (Experimental Clinic) H. Hager (p. 80) demonstrates the value of ophthalmodynamography in the control of the therapy for essential hypertension The brachial arterial pressure is not a reliable index of cerebral circulation it may be normal in response to Presinol treatment, whereas the cerebral blood pressure, as indicated by the arteria ophthalmica pressure may remain elevated or drops too rapidly In Part III (Vascular System and Arterial Hypertension) H J Holtmeier and C. Heilmeyer (p. 89) discuss the effect of diet, nutrition, and body weight on morbidity and mortality Statistical information on the changes in diet in Germany is traced back to 1850. The trend toward an increase in the intake of fat is similar to that in the United States. There is an abrupt decrease in morbidity from arterial hypertension during the war and an abrupt increase starting in 1948, and still continuing from 1960 to 1964 in excess of the prewar prevalence. The increase from 1936 to 1939 is not explained. The second part of this article is concerned with recent experiments on the interaction between reduction of NaCl and α-methyldopa. Many patients with essential hypertension lose their sensitivity to NaCl under treatment with α-methyldopa. Some new material on microinfarcts is presented by W. H. Hauss and G. Junge-Hulsing (p. 125) in the discussion of the well-established relationship between essential hypertension and myocardial infarction. E. Wollheim (p. 136) presents the results of extensive investigations on hepatic and renal blood flow in normotensive and hypertensive patients, against a background of general hemodynamics (circulating blood volume, cardiac minute volume peripheral resistance) and a consideration of age and weight.

A valuable critical discussion of the limitations of the indirect measurement of blood pressure is presented by H. Gillmann (p. 170) The relationship between width of cuff and circumference of arm is an important determinant for indirect measurement of blood pressure. It is of interest that in the largest German material so far collected (147,000 measurements) the blood pressure is higher in German middle-aged men than that found in United States samples. Consequently in American life insurance practice increased risk is assumed for values which are considered to be normal in Germany Gillmann suggests the possibility that the differences may be due in part to difference in cuff width, which raises the important question of international standardization of technique

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